Cell respiration

Anna Carratalà
anna.carratala@epfl.ch

- Carbon cycle
- Cell respiration
- Redox reactions
- Aerobic respiration
- Fermentation

Why Should Environmental Engineering Students Care About … Cell Respiration?

1. Core of Life’s Energy

- **Cellular respiration** is how organisms convert food into energy (ATP).
- Essential for understanding **biological energy flow**.

2. Impact on Ecosystems

- Cellular respiration influences the **carbon cycle**.
- Helps in understanding how **living organisms contribute to carbon emissions** and how ecosystems balance energy and matter.

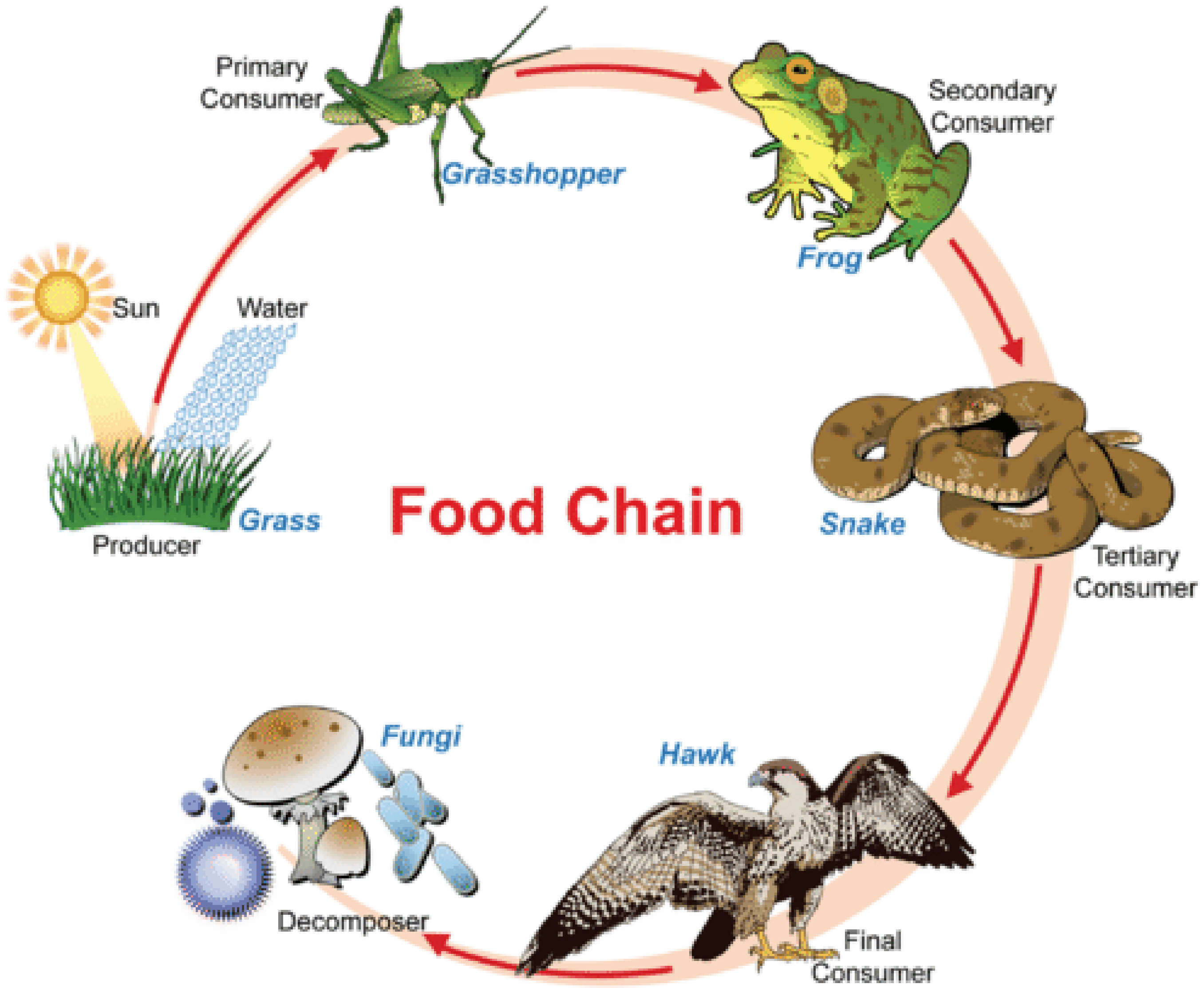
3. Relevance to Pollution & Climate Change

- By-products like **CO2** affect global **greenhouse gas levels**.
- Knowing respiration helps analyze **impacts on the environment** and design solutions for reducing emissions.

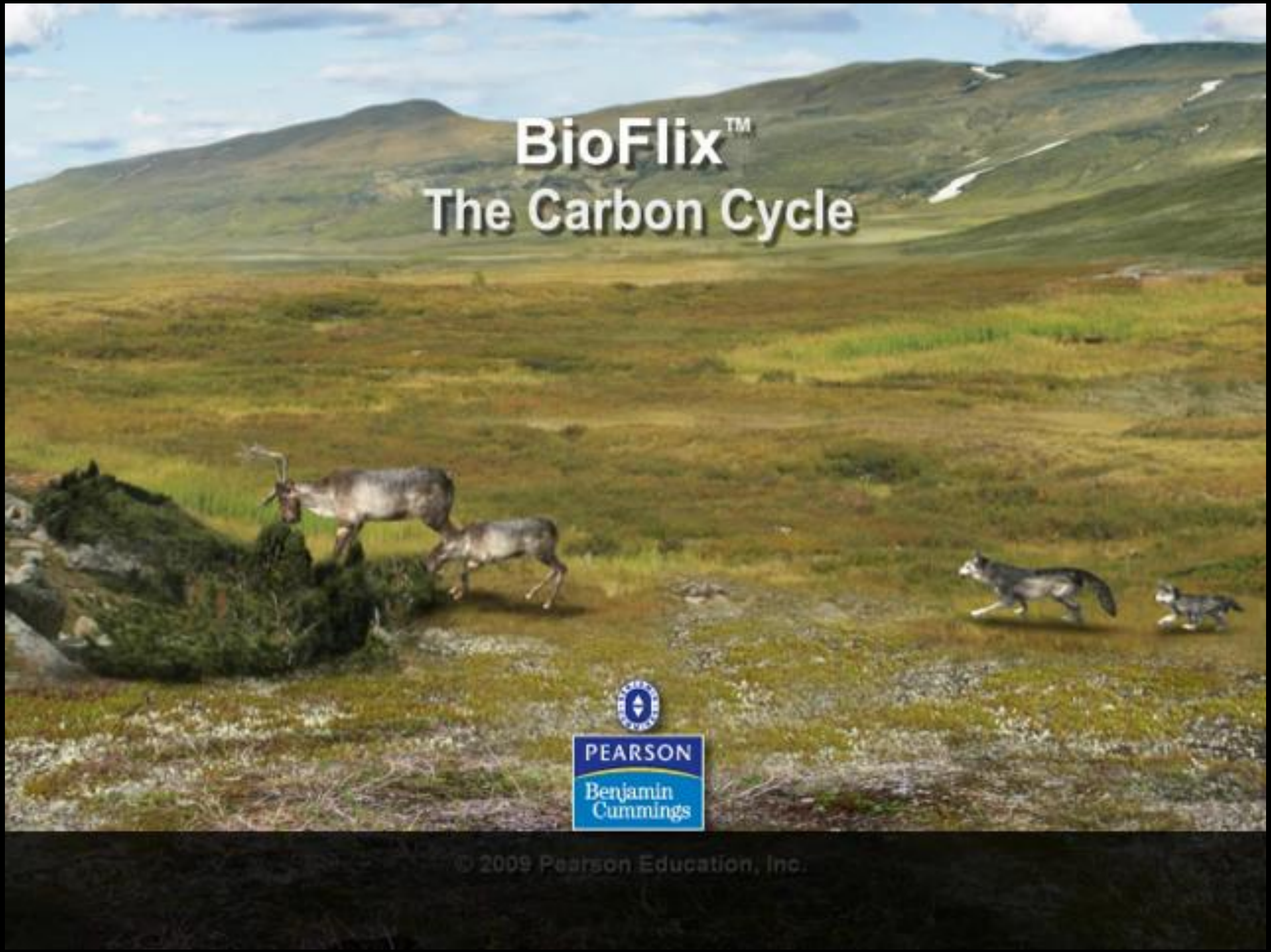
Recap: life is work, work needs energy

- Living cells require energy from outside sources to do work
- The work of the cell includes assembling polymers, membrane transport, moving, reproducing…
- Animals can obtain energy to do this work by **feeding** on other animals, organic compounds, or photosynthetic organisms (*heterotrophic*).
- Photosynthetic organisms use the energy of sunlight to synthetize organic compounds (*autotrophic*).

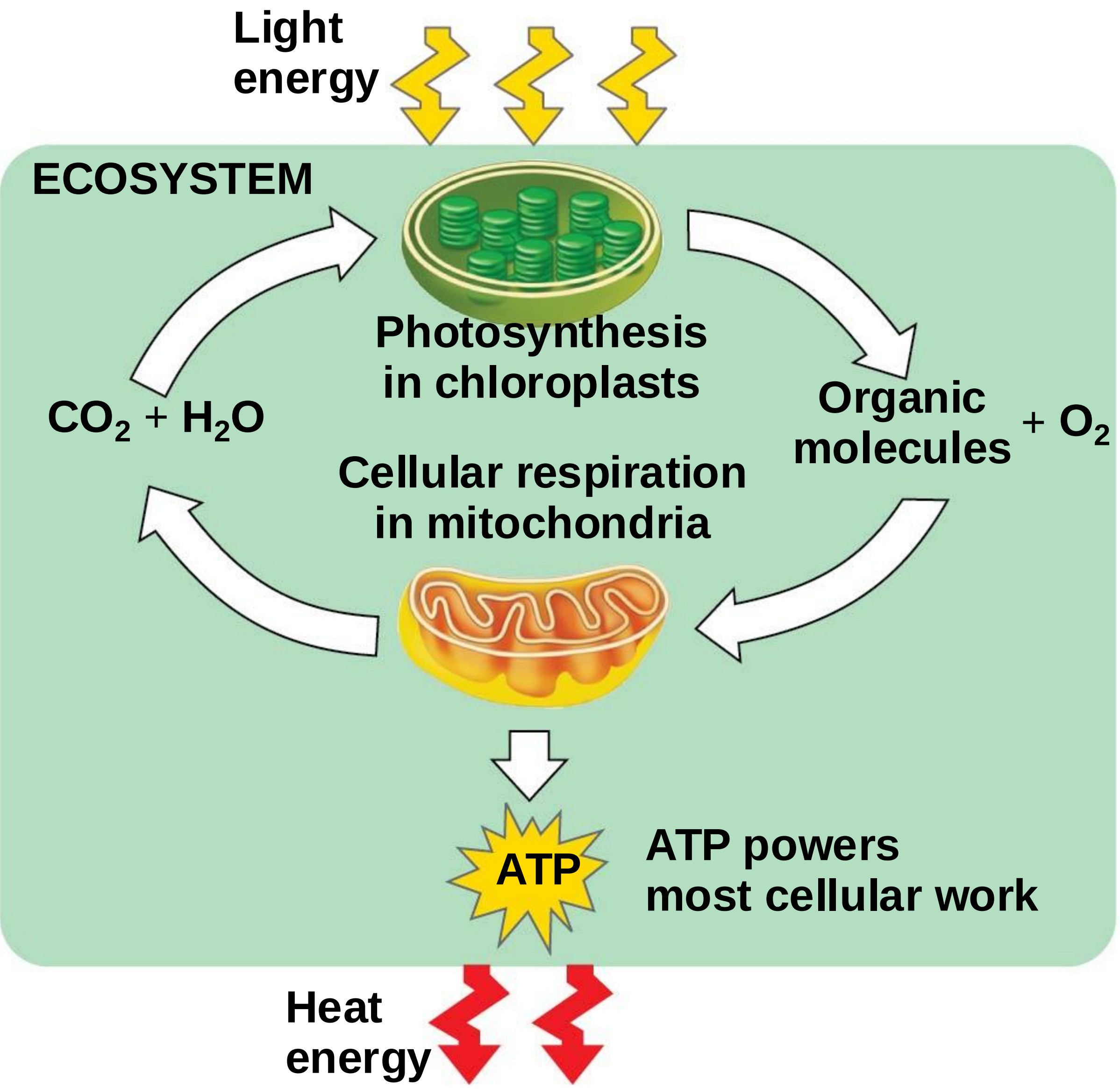
An example of a trophic chain



Background: the Carbon Cycle

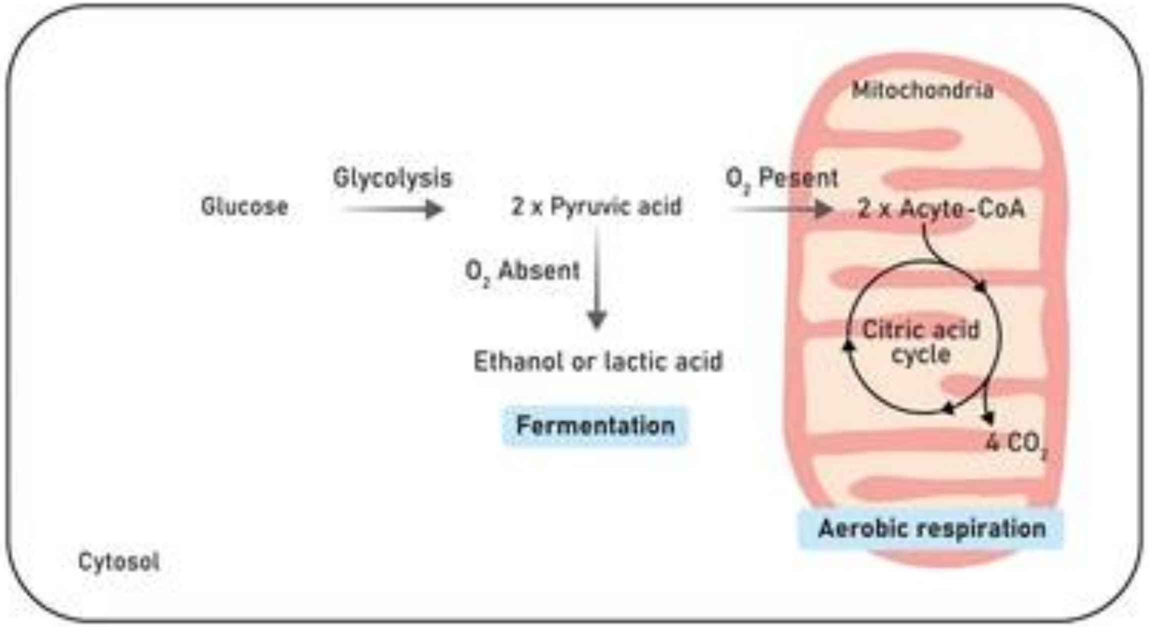


Energy flow and chemical recycling in ecosystems



Catabolic Pathways and Production of ATP

- The breakdown of organic molecules is exergonic
- **Aerobic respiration** requires organic molecules and O_2 and yields ATP
- **Fermentation** is a partial degradation of sugars that occurs without O_2
- **Anaerobic respiration** is similar to aerobic respiration but is based on compounds other than O_2 (occurs without oxygen)

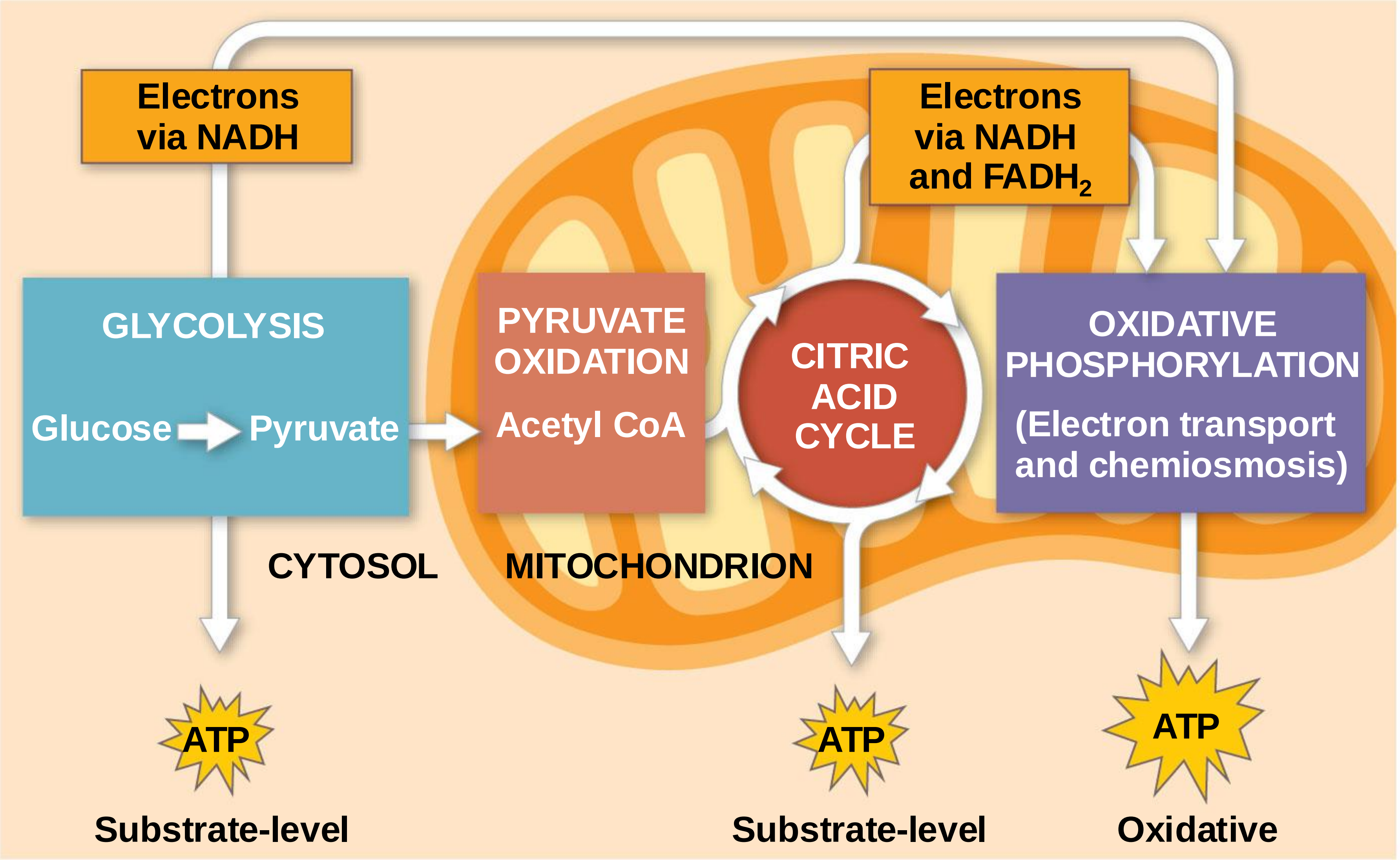


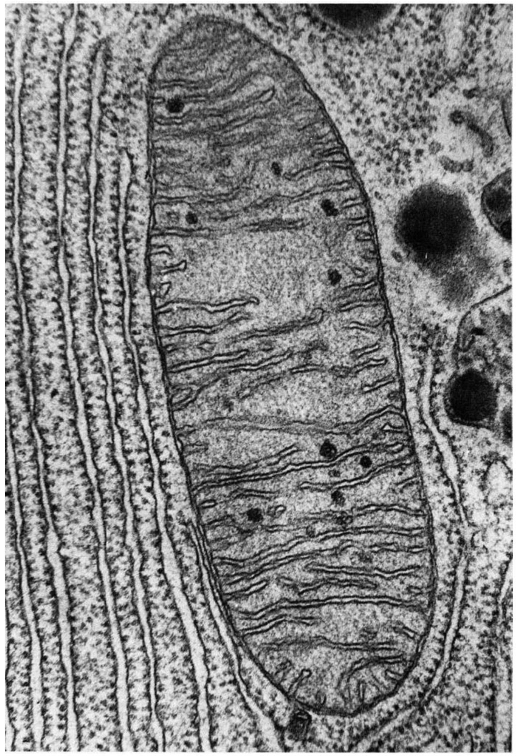
Cellular respiration

- **Cellular respiration** is the process through which cells generate energy in the form of adenosine triphosphate (ATP) by breaking down organic molecules such as glucose. It mostly occurs within the mitochondria of eukaryotic cells and involves a series of biochemical reactions.
- Cellular respiration includes both aerobic and anaerobic respiration but is often used to refer to aerobic respiration
- Although carbohydrates, fats, and proteins are all consumed as fuel, it is helpful to trace cellular respiration with the sugar glucose

$$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O + \text{Energy (ATP + heat)}$$

Cellular respiration: overview





Mithocondria under the microscope

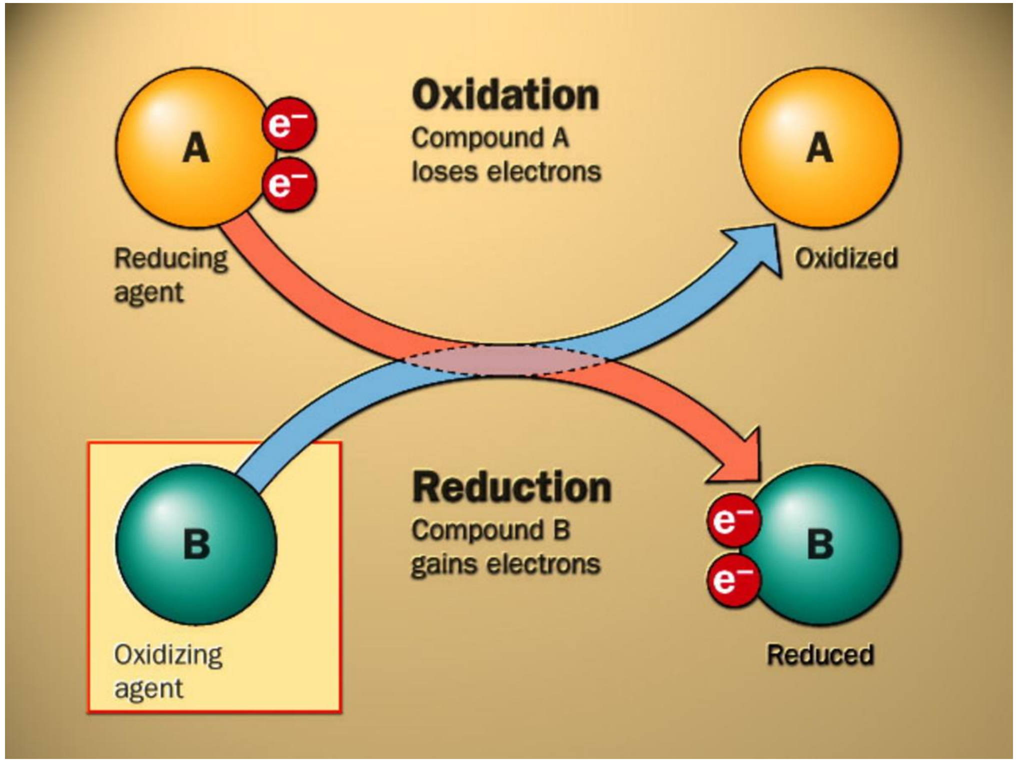
Relationship between glucose and ATP

- We can use money as an analogy for cellular respiration:
  - Glucose is like a larger-denomination bill—it is worth a lot, but it is hard to spend
  - ATP is like a number of smaller-denomination bills of equivalent value—they can be spent more easily
  - Cellular respiration cashes in a large denomination of energy (glucose) for the small change of many molecules of ATP

Cellular respiration is based on a series of redox reactions

Redox Reactions: Oxidation and Reduction

- Cellular respiration is based on redox reactions
- The transfer of electrons during chemical reactions releases energy stored in organic molecules
- This released energy is ultimately used to synthesize ATP.



OIL RIG

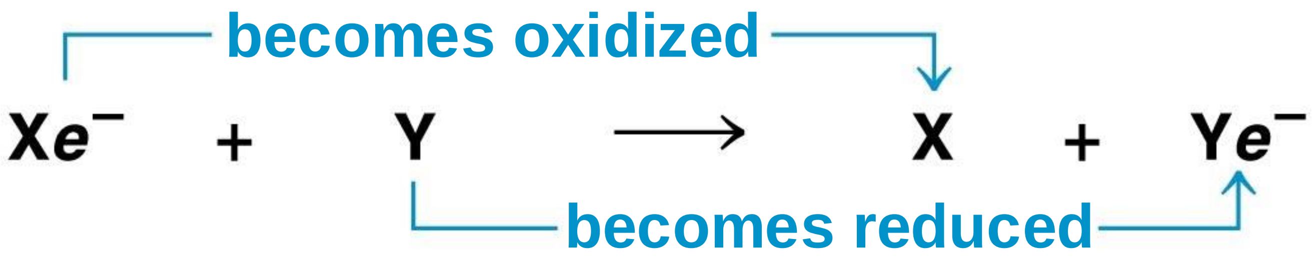
OIL RIG

OIL RIG

OIL: Oxidation is loss of electrons
RIG: Reduction is gain of electrons

The Principle of Redox

- Chemical reactions that transfer electrons between reactants are called oxidation-reduction reactions, or **redox reactions**
- In **oxidation**, a substance loses electrons, or is oxidized
- In **reduction**, a substance gains electrons, or is reduced (the amount of positive charge is reduced)

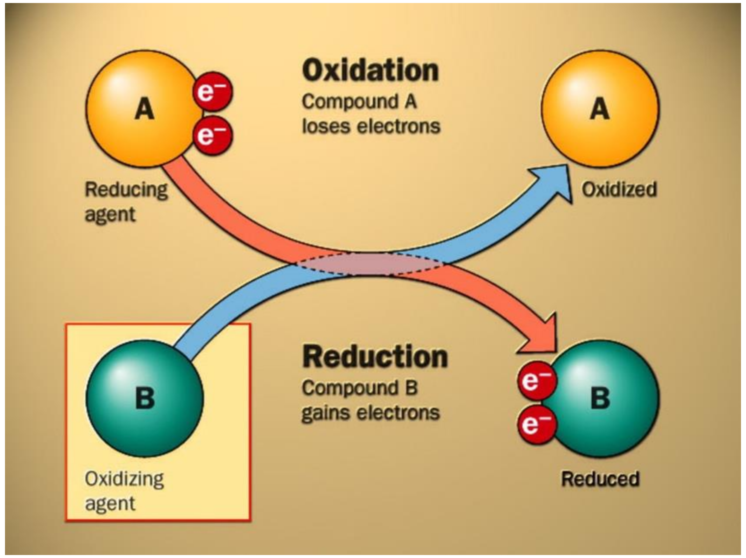


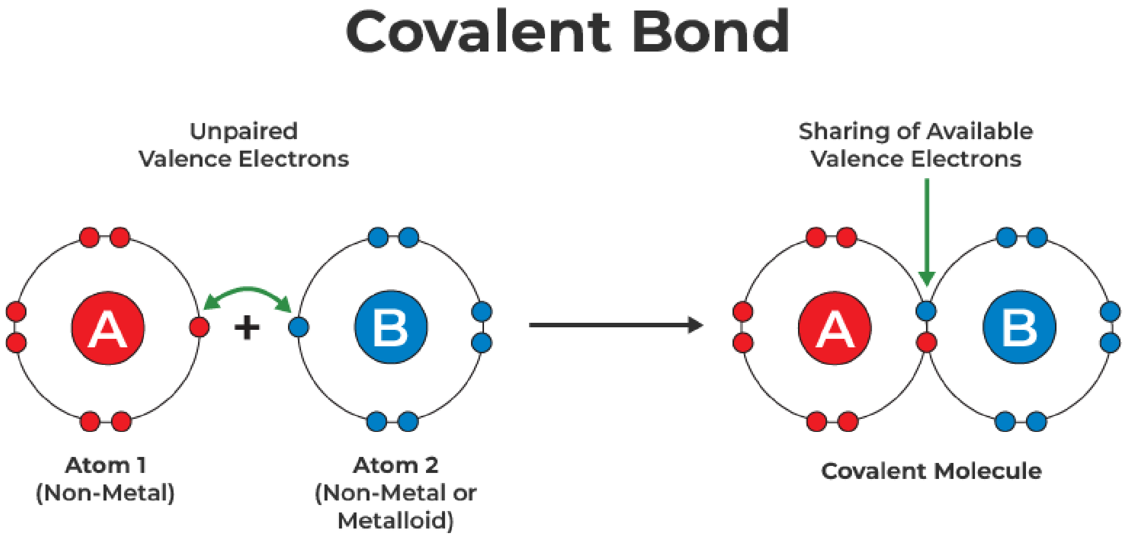
becomes oxidized

$$Xe^- + Y \longrightarrow X + Ye^-$$

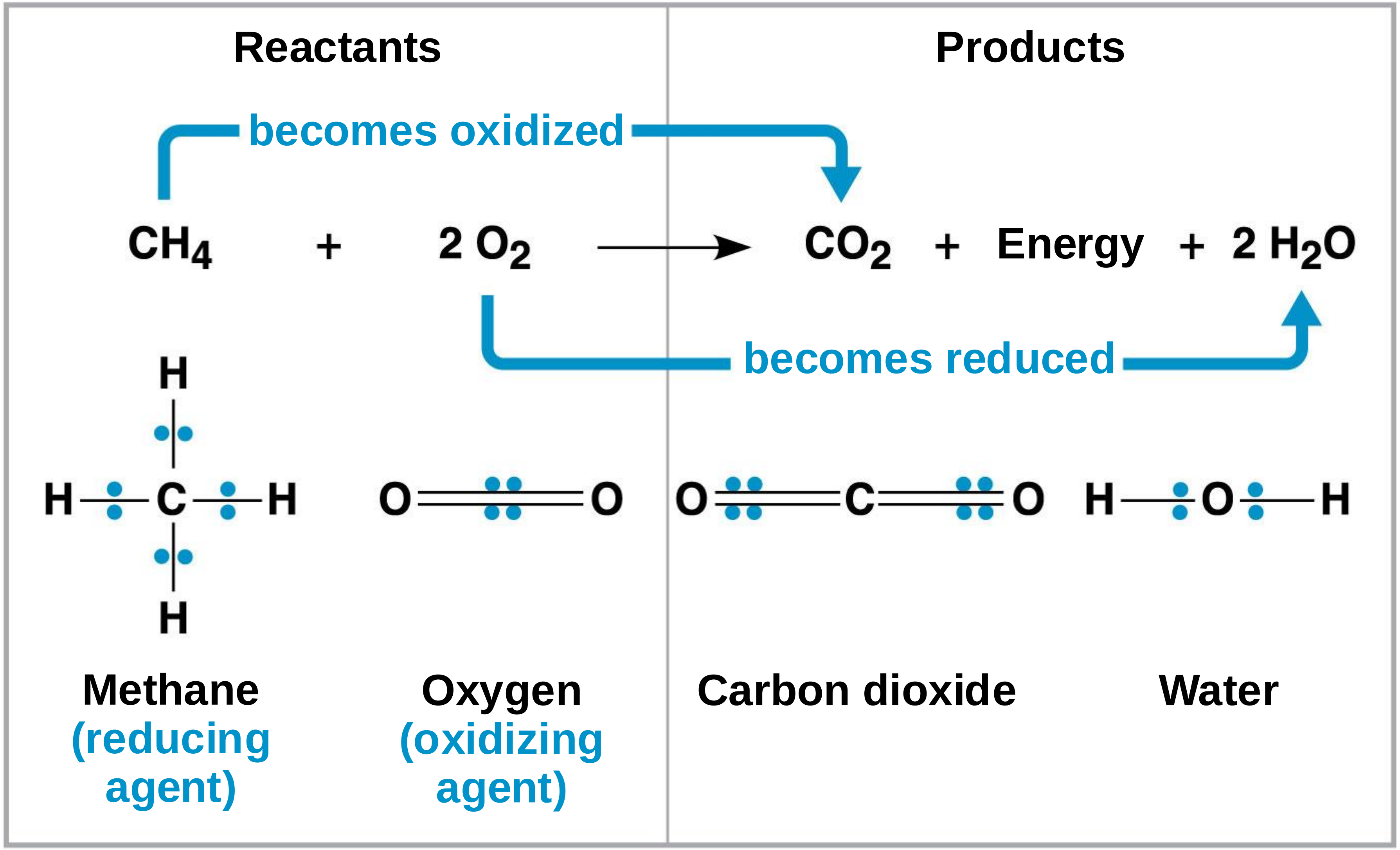
becomes reduced

- The electron donor is called the **reducing agent**
- The electron receptor is called the **oxidizing agent**
- Some redox reactions do not transfer electrons but change the electron sharing in covalent bonds
- An example is the reaction between methane and O_2





Example methane and O_2 combustion



Reactants

Products

becomes oxidized

$CH_4 + 2\,O_2 \longrightarrow CO_2 + \text{Energy} + 2\,H_2O$

becomes reduced

Methane
(reducing agent)

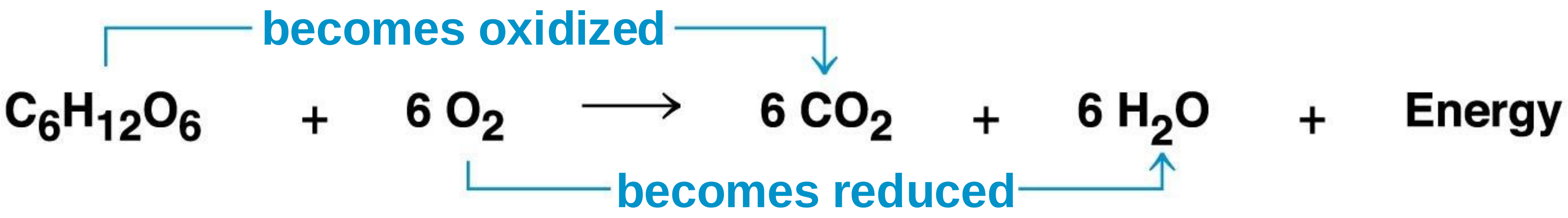
Oxygen
(oxidizing agent)

Carbon dioxide

Water

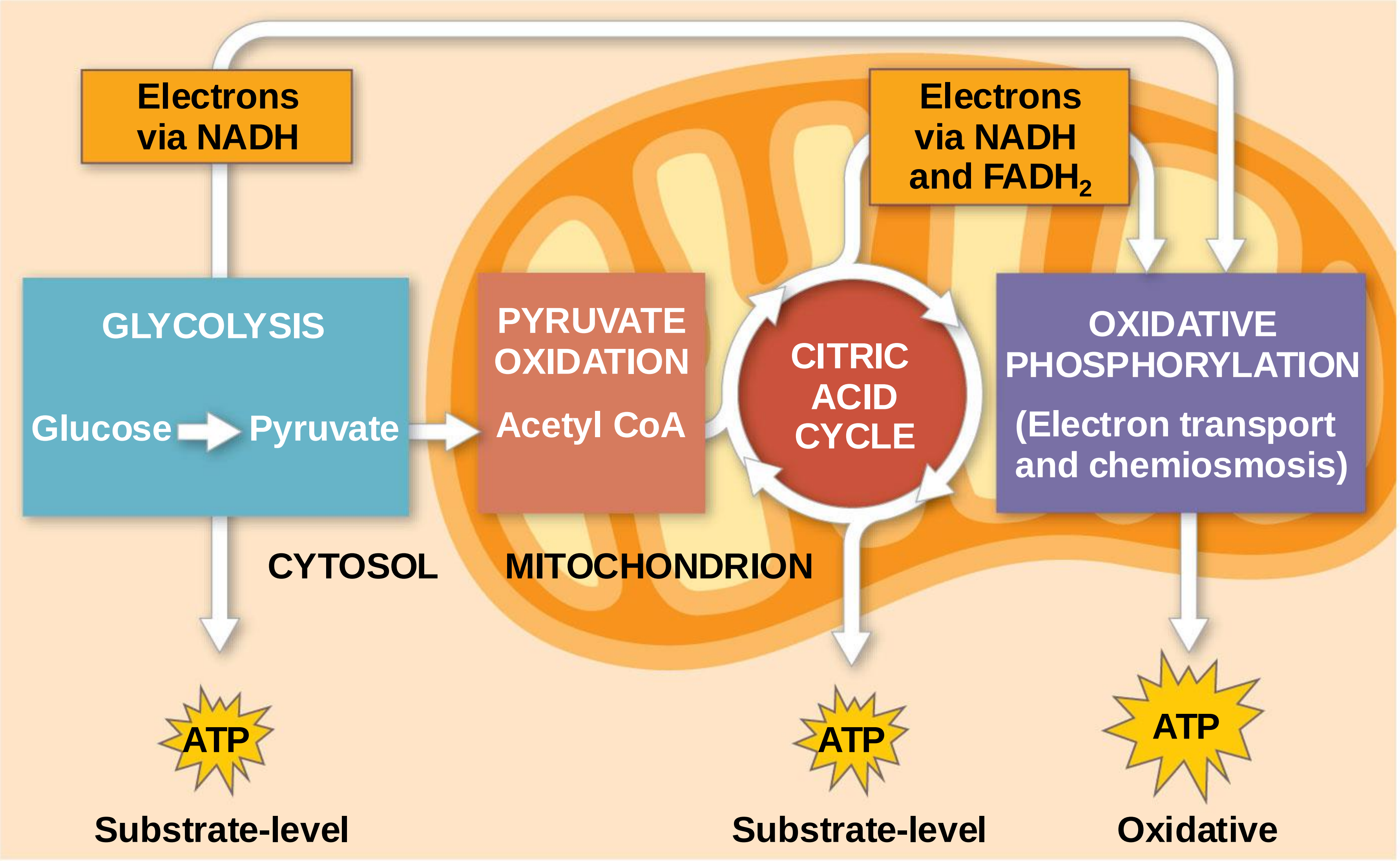
Oxidation of organic molecules as fuel during cellular respiration

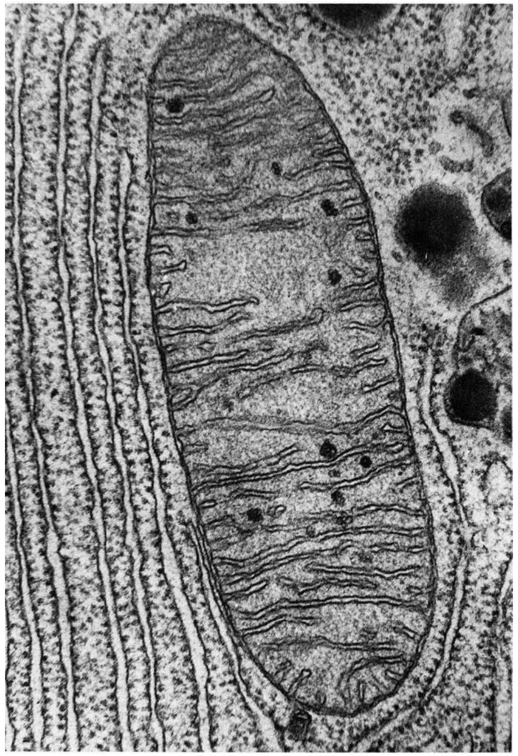
- During cellular respiration, the fuel (such as glucose) is oxidized, and O_2 is reduced
- Organic molecules with an abundance of hydrogen are excellent sources of high-energy electrons
- Energy is released as the electrons associated with hydrogen ions are transferred to oxygen, a lower energy state



$$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O + \text{Energy}$$

Cellular respiration: NAD+ and NADH

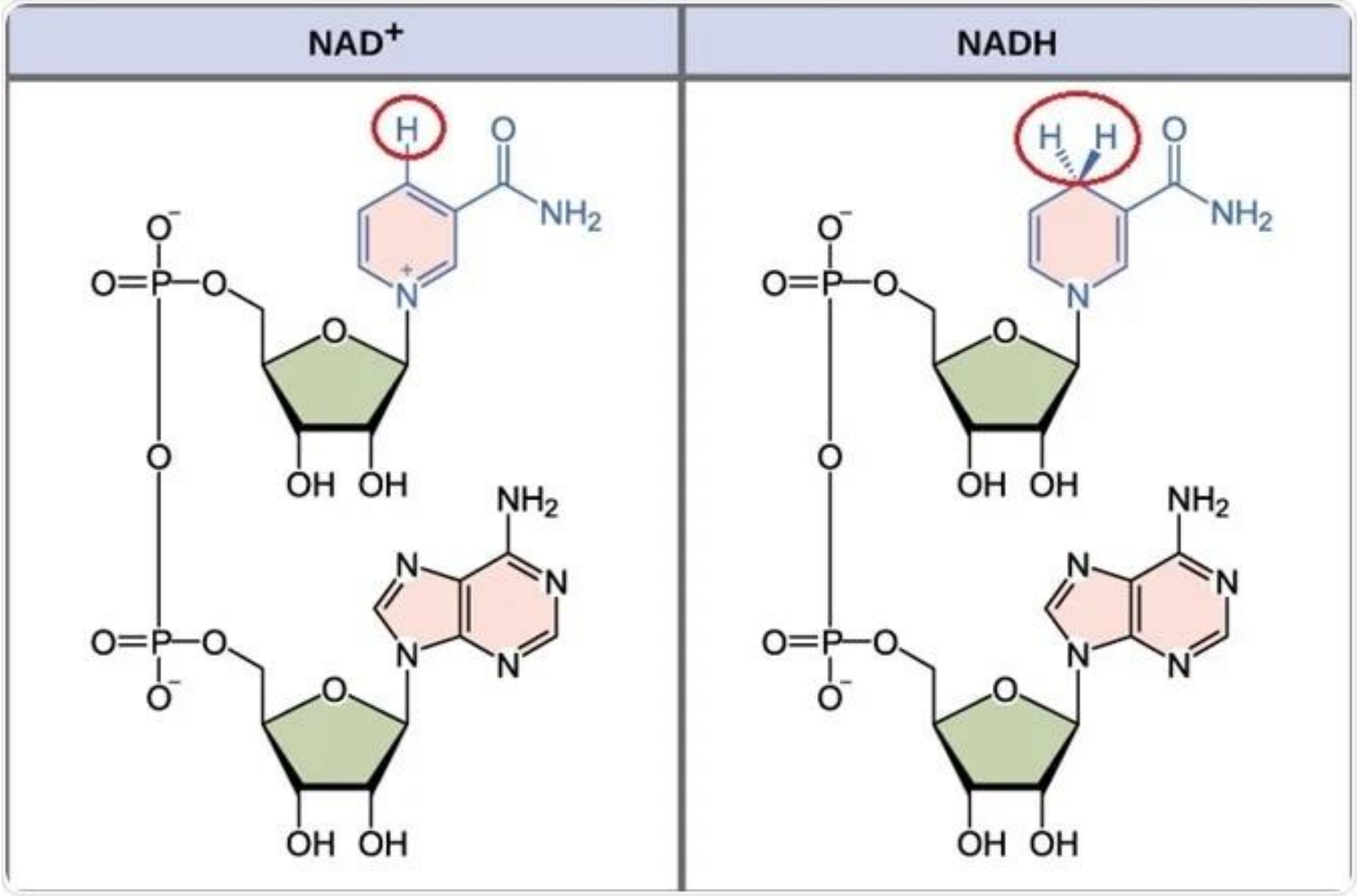




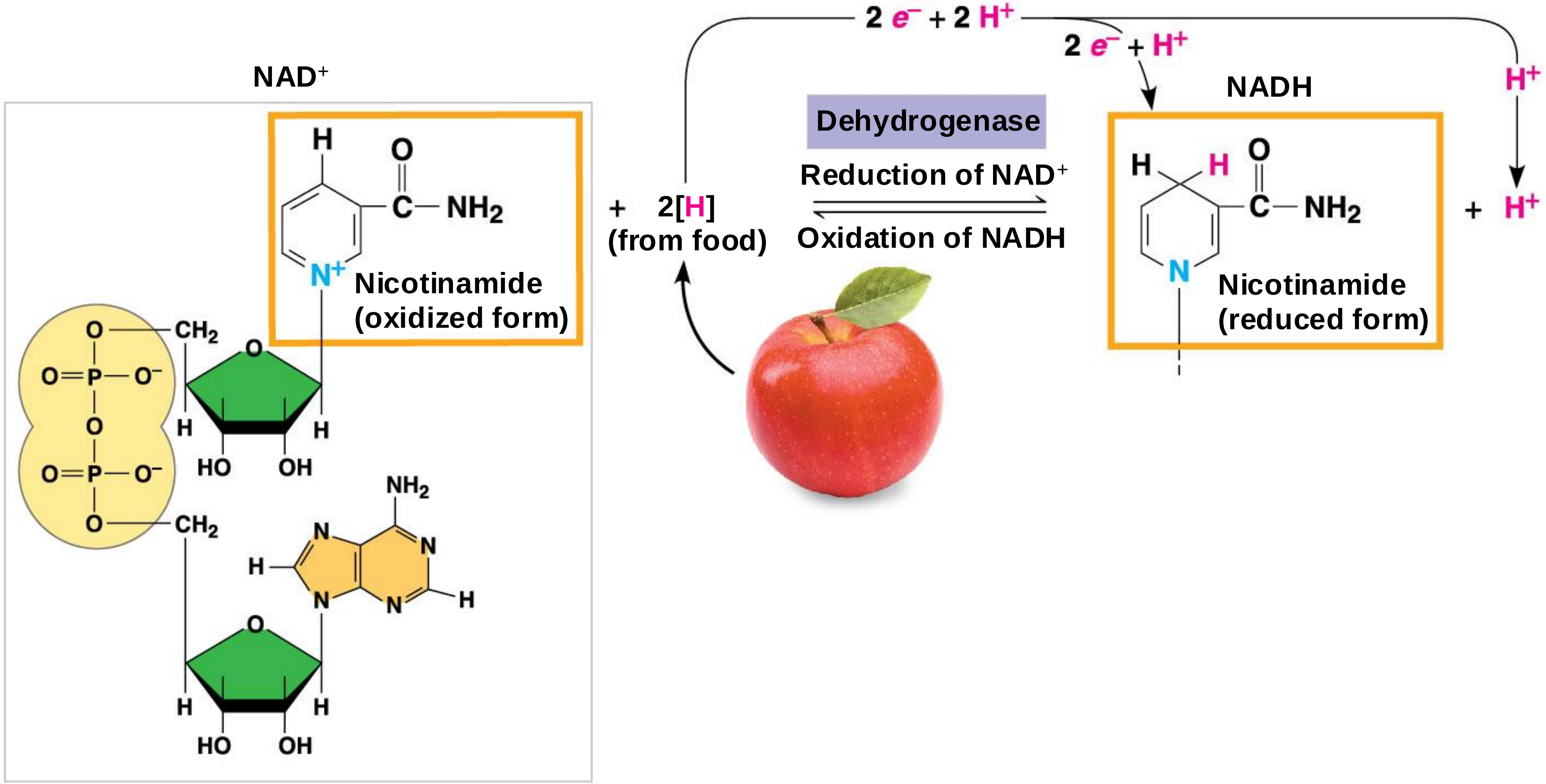
Mithocondria under the microscope

Energy Harvest via NAD$^+$ and the Electron Transport Chain

- In cellular respiration, glucose and other organic molecules are broken down in a series of steps
- Electrons from organic compounds are usually first transferred to **NAD$^+$**, a coenzyme
- As an electron acceptor, NAD$^+$ functions as an oxidizing agent during cellular respiration
- Each NADH (the reduced form of NAD$^+$) represents stored energy that is tapped to synthesize ATP



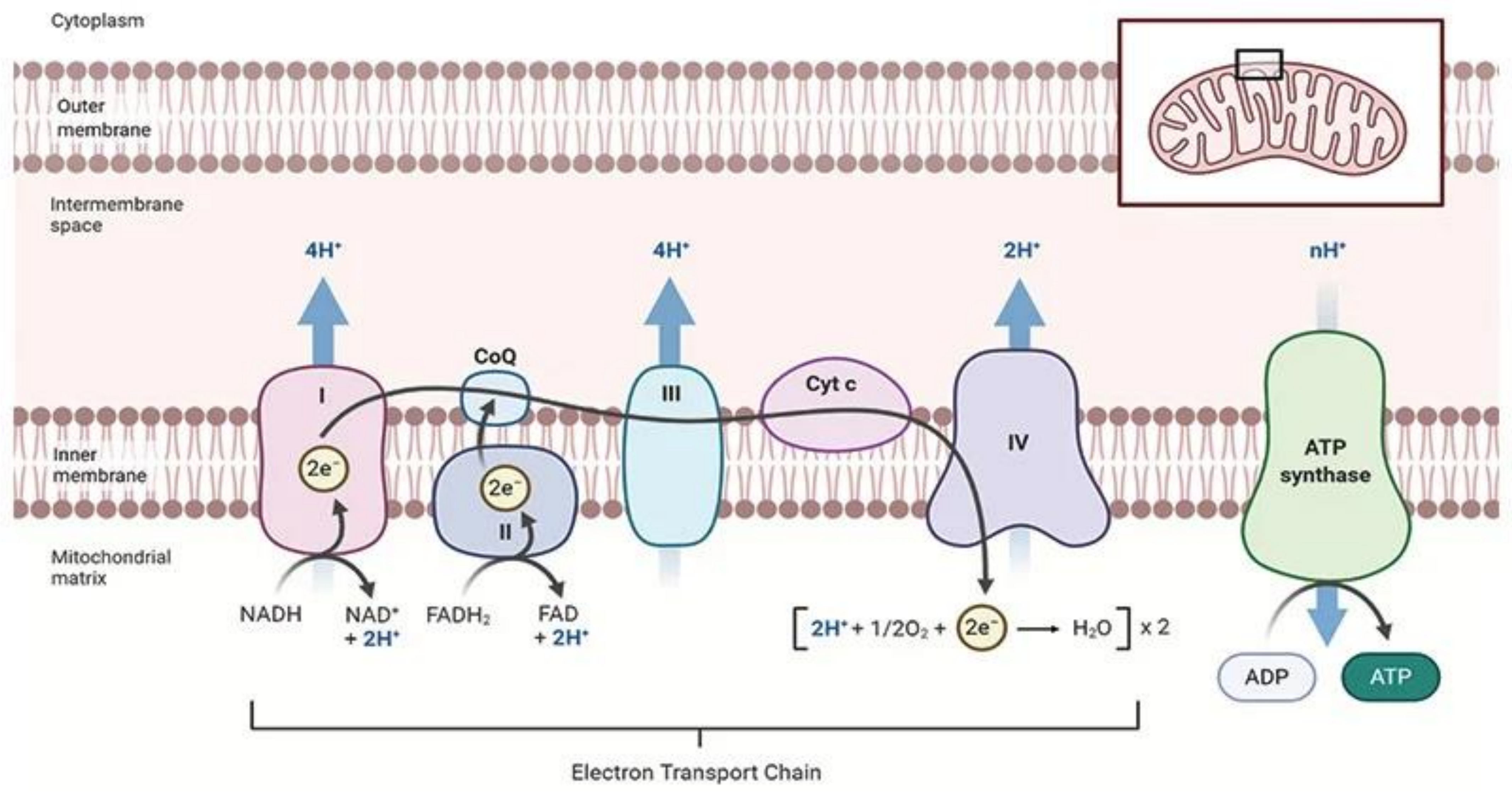
NAD$^+$ as an electron shuttle



NAD^+ as an electron shuttle

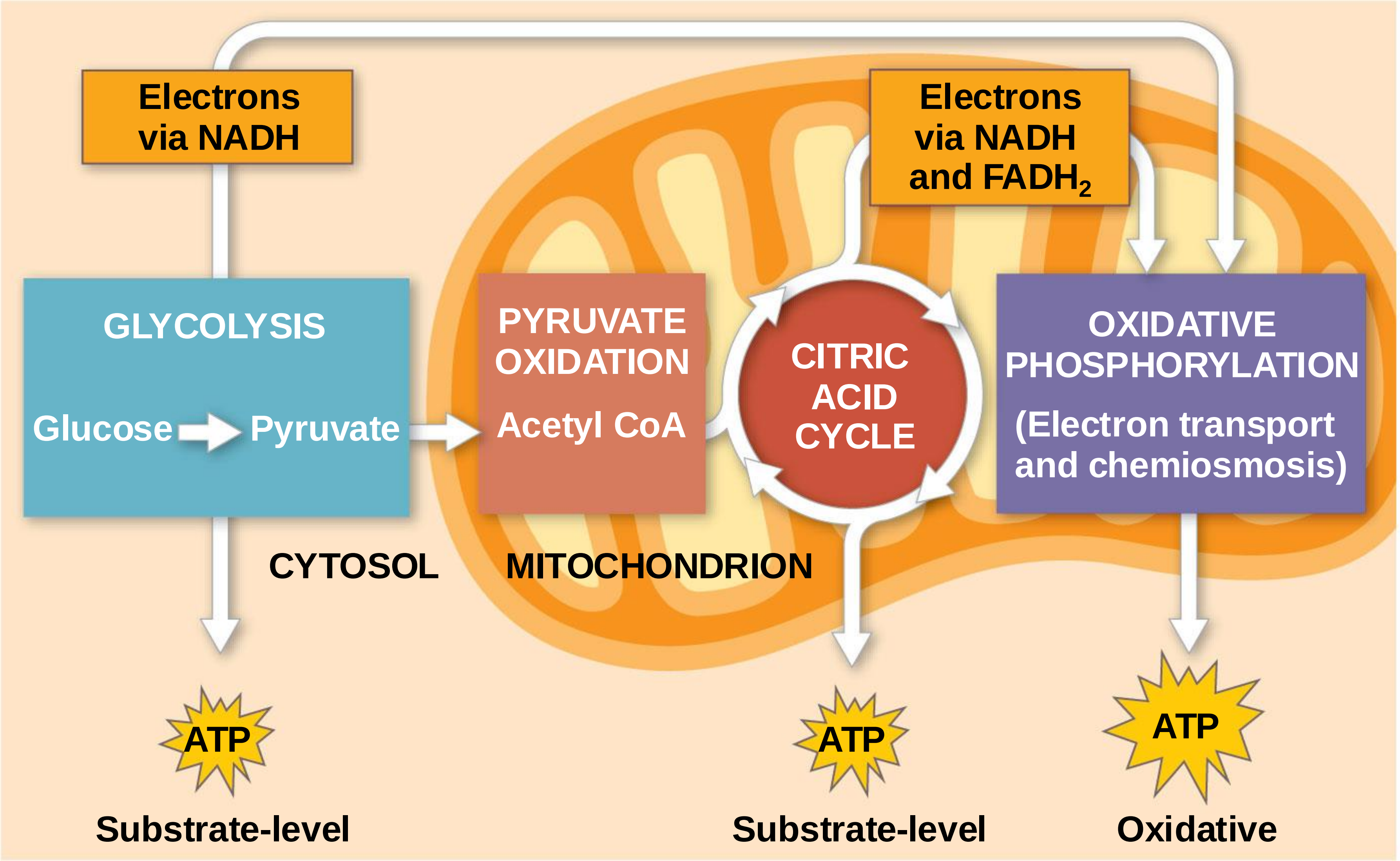
- NADH passes the electrons to the **electron transport chain**
- Unlike an uncontrolled reaction, the electron transport chain passes electrons in a series of steps
- O_2 pulls electrons down the chain in an energy-yielding tumble
- The energy yielded is used to regenerate ATP

Electron transport chain



Zooming into the cellular respiration

Cellular respiration: overview

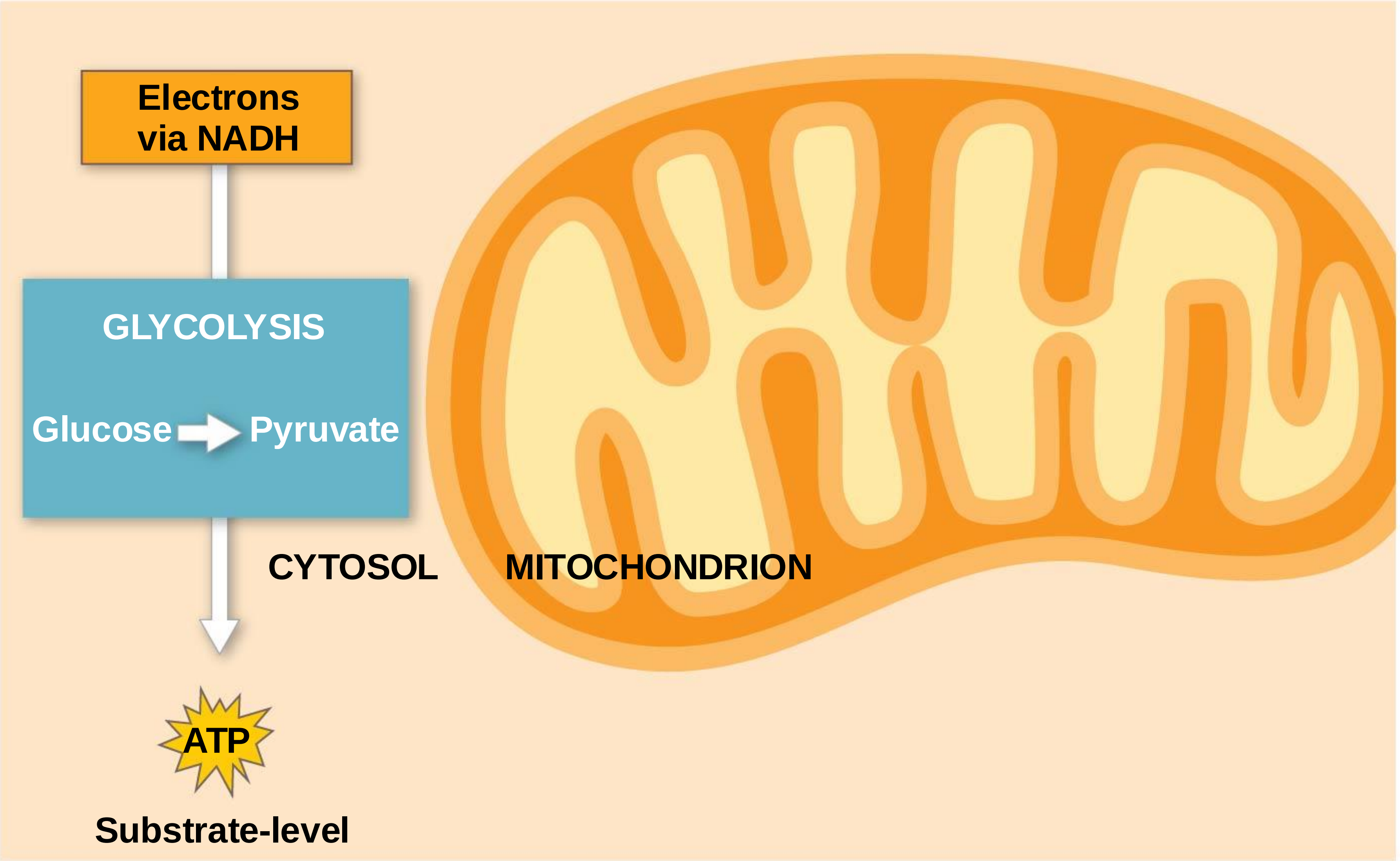


The Stages of Cellular Respiration: *A Preview*

- Harvesting of energy from glucose has three stages
  1. **Glycolysis** (breaks down glucose into two molecules of pyruvate)
  2. The **citric acid cycle** (completes the breakdown of glucose)
  3. **Oxidative phosphorylation** (accounts for most of the ATP synthesis)

Color coding in the figures hereafter

1. **GLYCOLYSIS (color-coded blue throughout the chapter)**
2. **PYRUVATE OXIDATION and the CITRIC ACID CYCLE (color-coded light orange and dark orange)**
3. **OXIDATIVE PHOSPHORYLATION: Electron transport and chemiosmosis (color-coded purple)**



Electrons
via NADH

GLYCOLYSIS

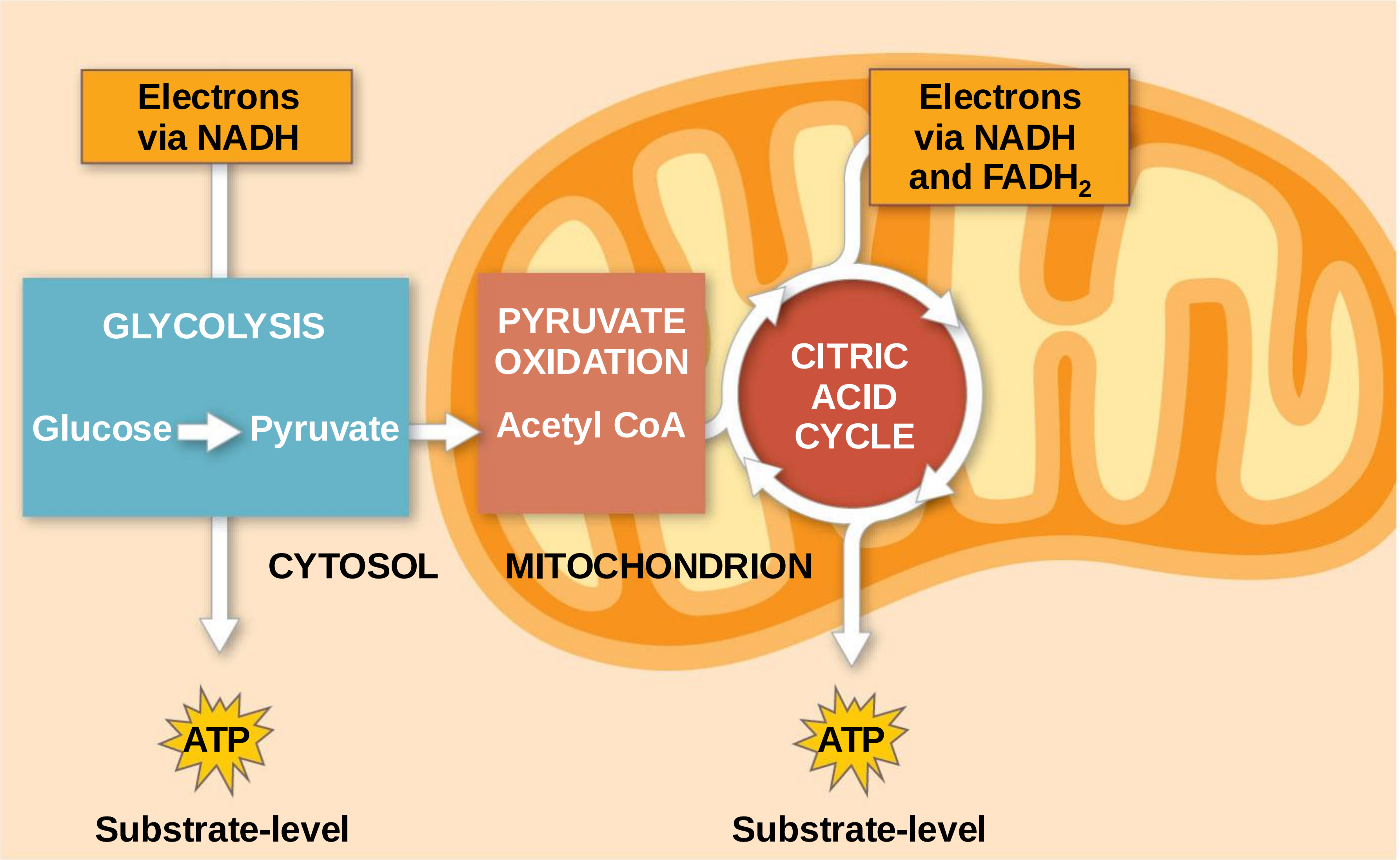
Glucose → Pyruvate

CYTOSOL

MITOCHONDRION

ATP

Substrate-level



Electrons via NADH

GLYCOLYSIS

Glucose → Pyruvate

PYRUVATE OXIDATION

Acetyl CoA

CITRIC ACID CYCLE

Electrons via NADH and $FADH_2$

CYTOSOL

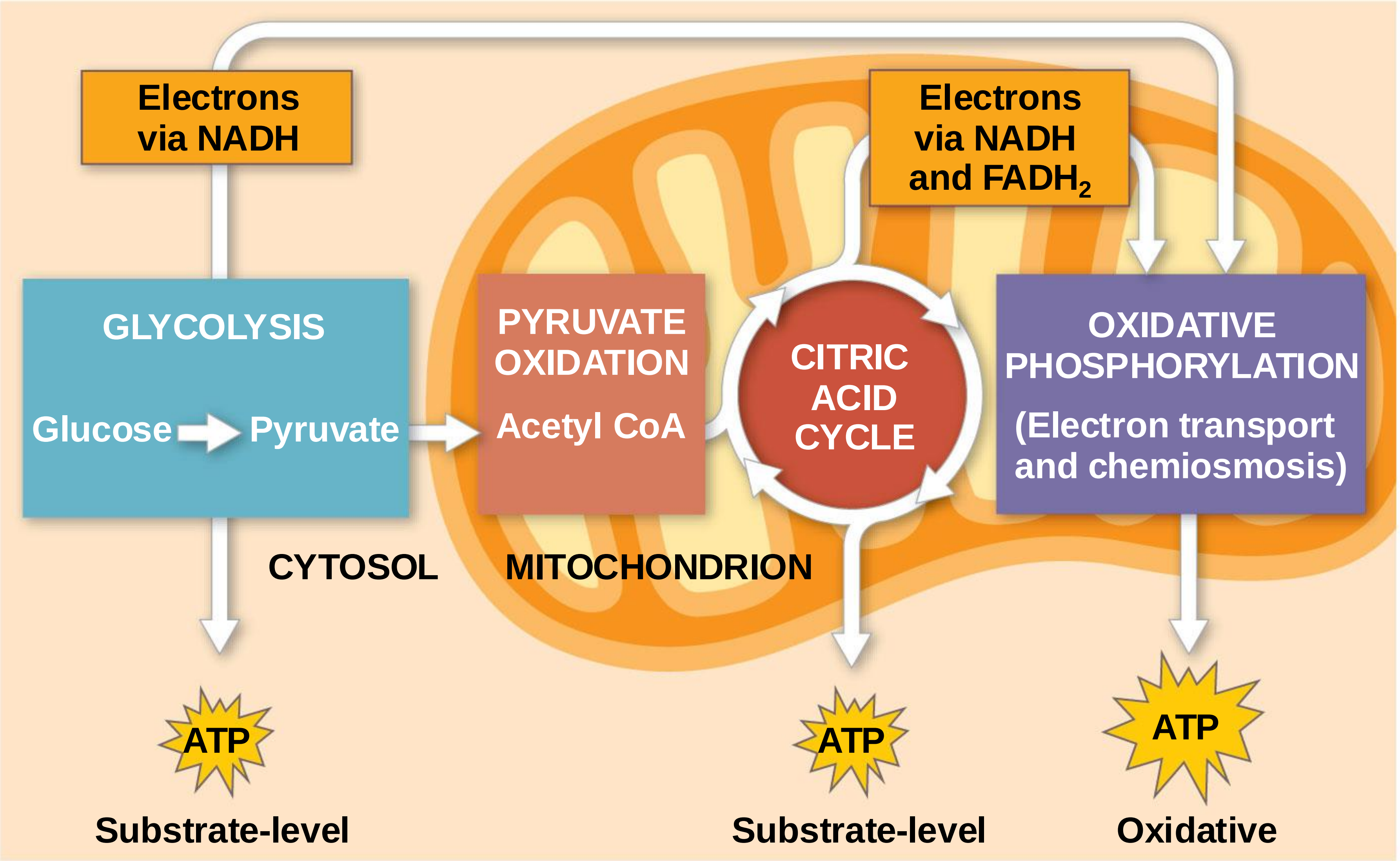
MITOCHONDRION

ATP

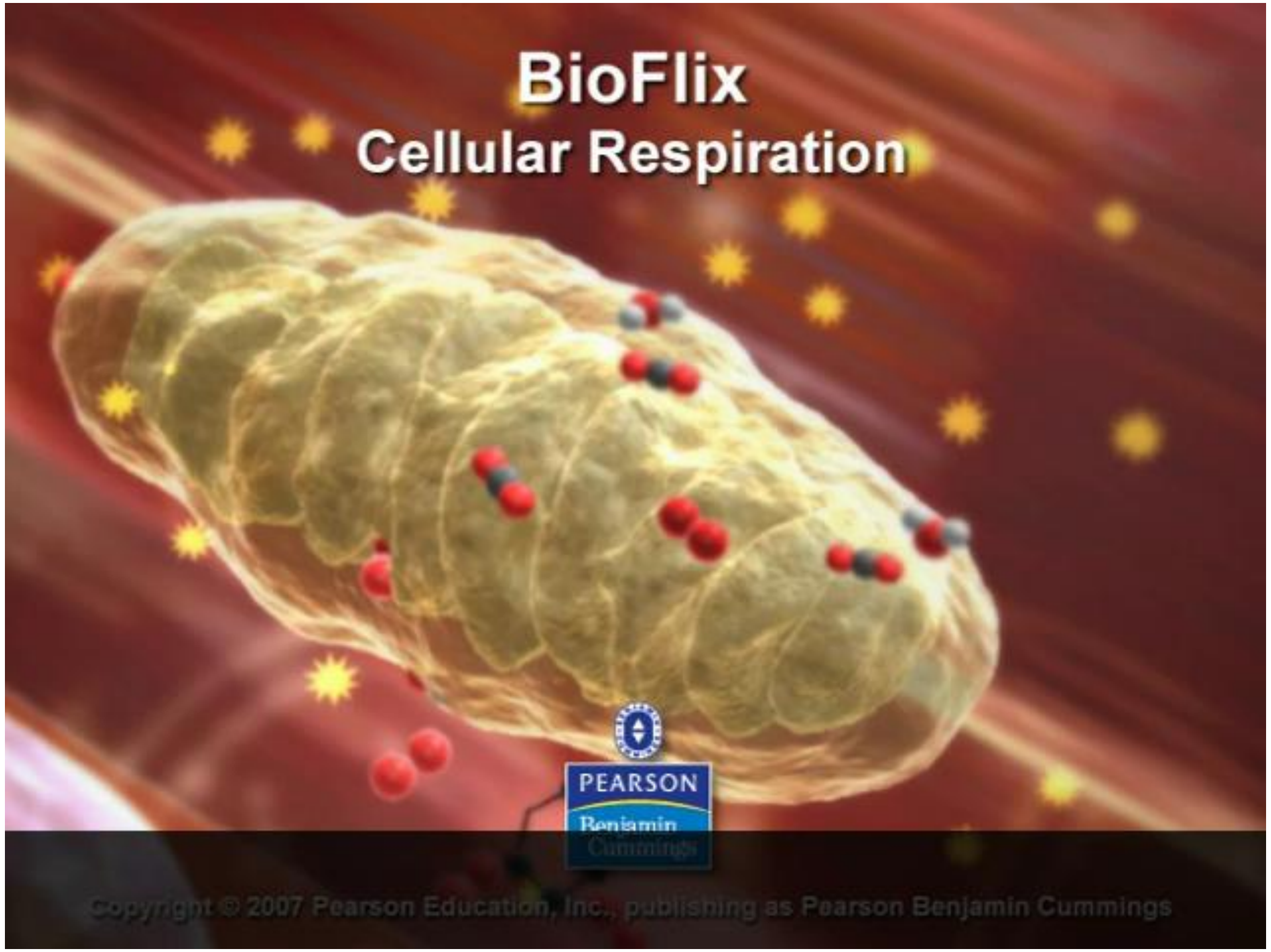
Substrate-level

ATP

Substrate-level

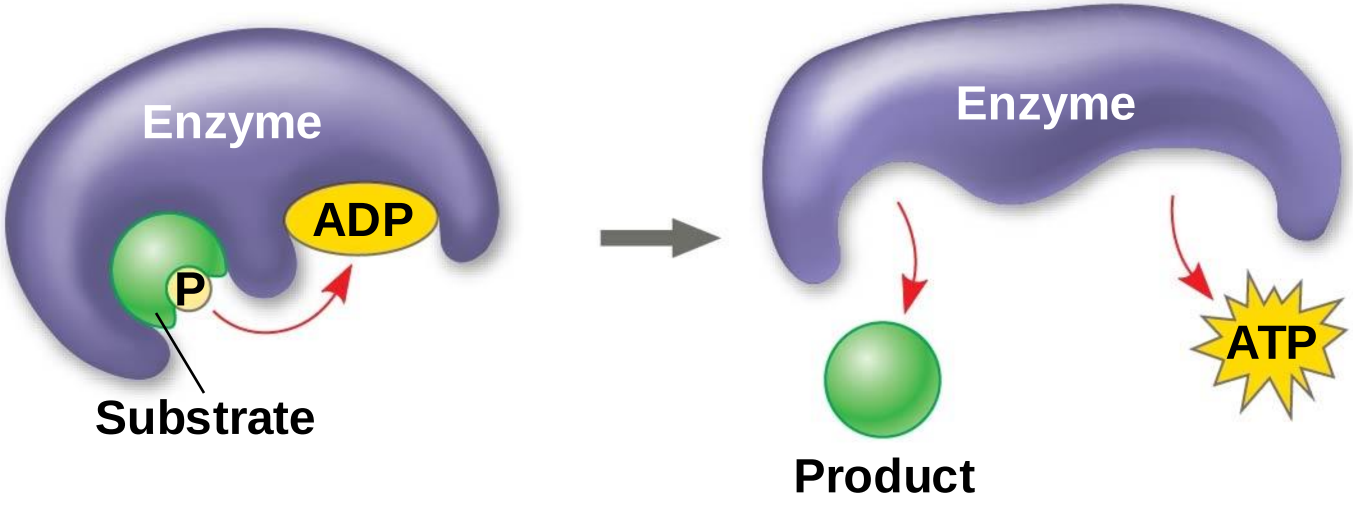

Electrons via NADH
Electrons via NADH and FADH$_2$
GLYCOLYSIS
Glucose
Pyruvate
PYRUVATE OXIDATION
Acetyl CoA
CITRIC ACID CYCLE
OXIDATIVE PHOSPHORYLATION
(Electron transport and chemiosmosis)
CYTOSOL
MITOCHONDRION
ATP
ATP
ATP
Substrate-level
Substrate-level
Oxidative

Cellular Respiration



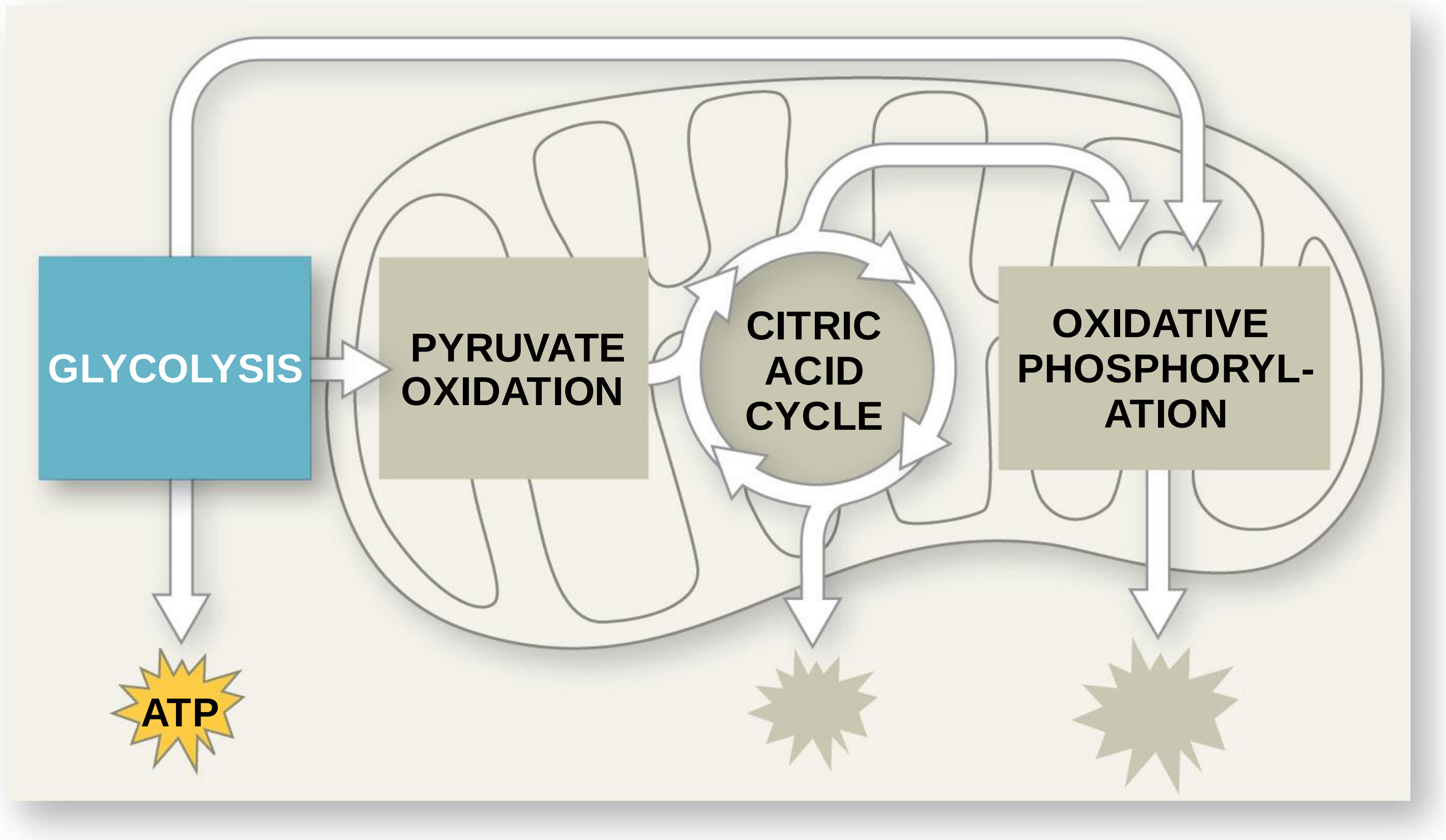
ATP regeneration

- The process that generates almost 90% of the ATP is called **oxidative phosphorylation** because it is powered by redox reactions
- A smaller amount of ATP is formed in glycolysis and the citric acid cycle by **substrate-level phosphorylation**



For each molecule of glucose degraded to CO_2 and water by respiration, the cell makes up to **32 molecules of ATP (30-32 actually)**

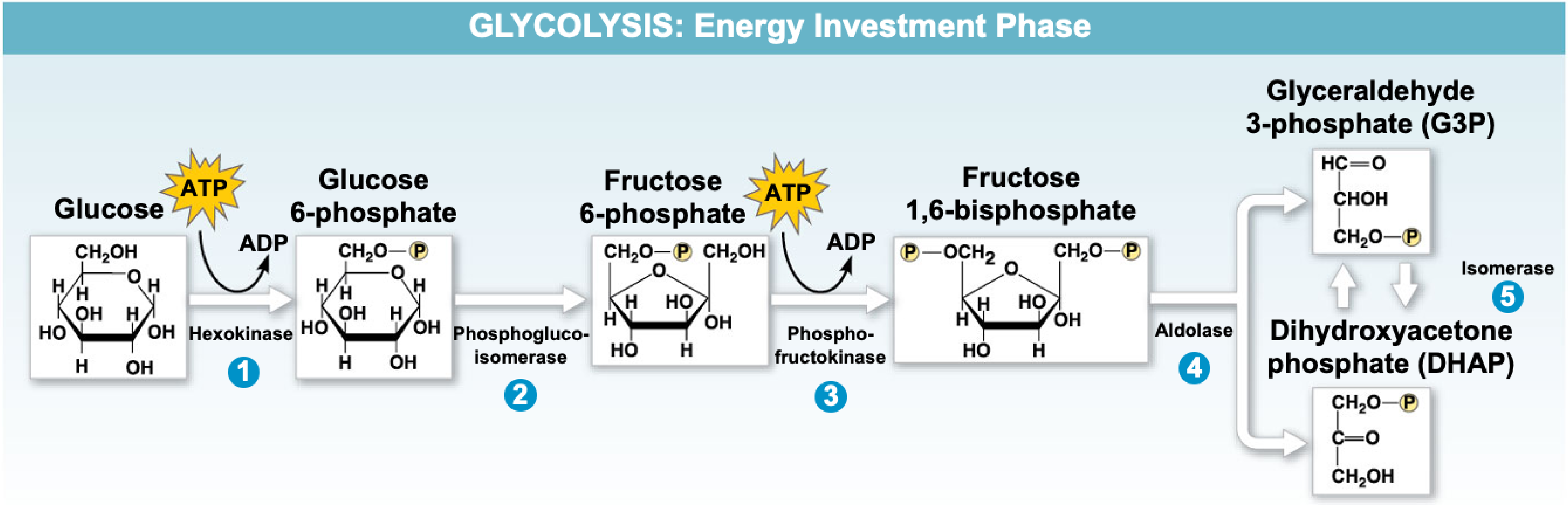
Zooming into the cellular respiration: glycolysis


GLYCOLYSIS
PYRUVATE OXIDATION
CITRIC ACID CYCLE
OXIDATIVE PHOSPHORYL-ATION
ATP

Glycolysis harvests chemical energy by oxidizing glucose to pyruvate

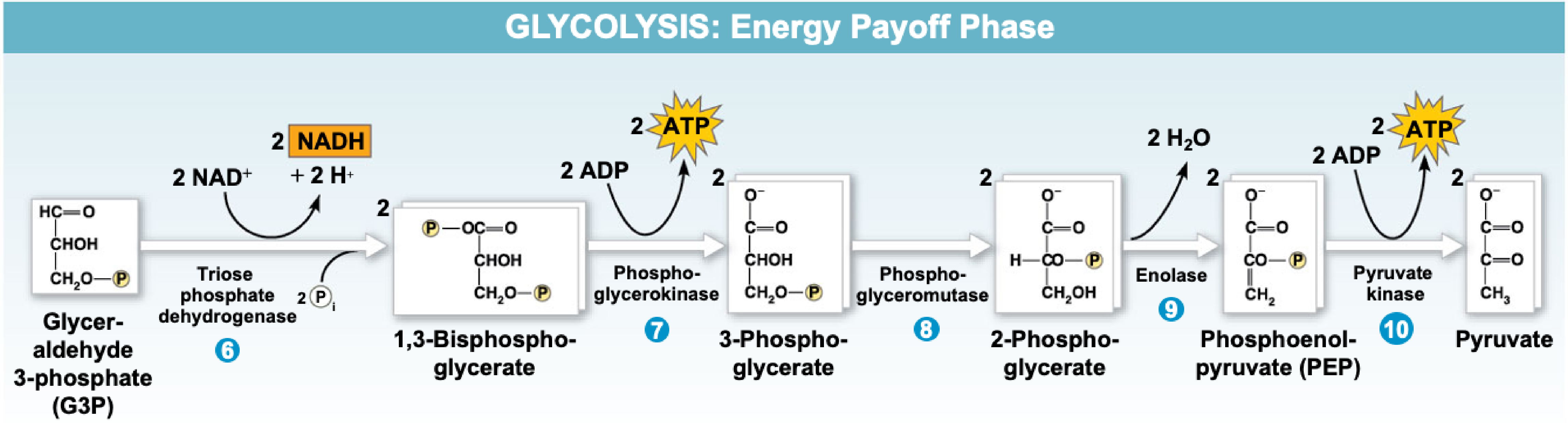
- Glycolysis (“sugar splitting”) breaks down glucose into two molecules of pyruvate
- Glycolysis occurs in the **cytoplasm** and has two major phases
  - Energy investment phase
  - Energy payoff phase
- Glycolysis occurs whether or not O_2 is present

A closer look at glycolysis (part 1: investment phase)



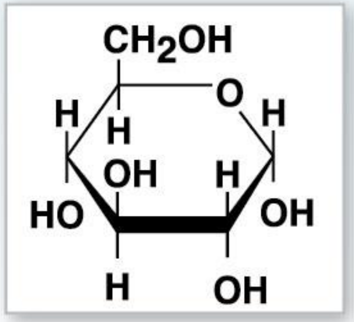
Hexokinase, phosphogluco-isomerase, phosphofructokinase, aldolase and isomerase are the **enzymes** involved in the glycolysis (part I).

A closer look at glycolysis (part 2: payoff phase)

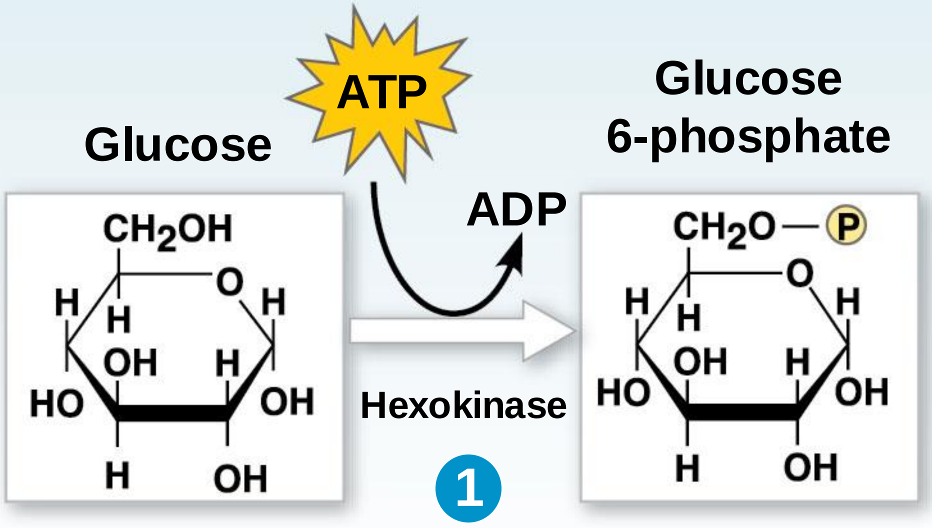


GLYCOLYSIS: Energy Investment Phase

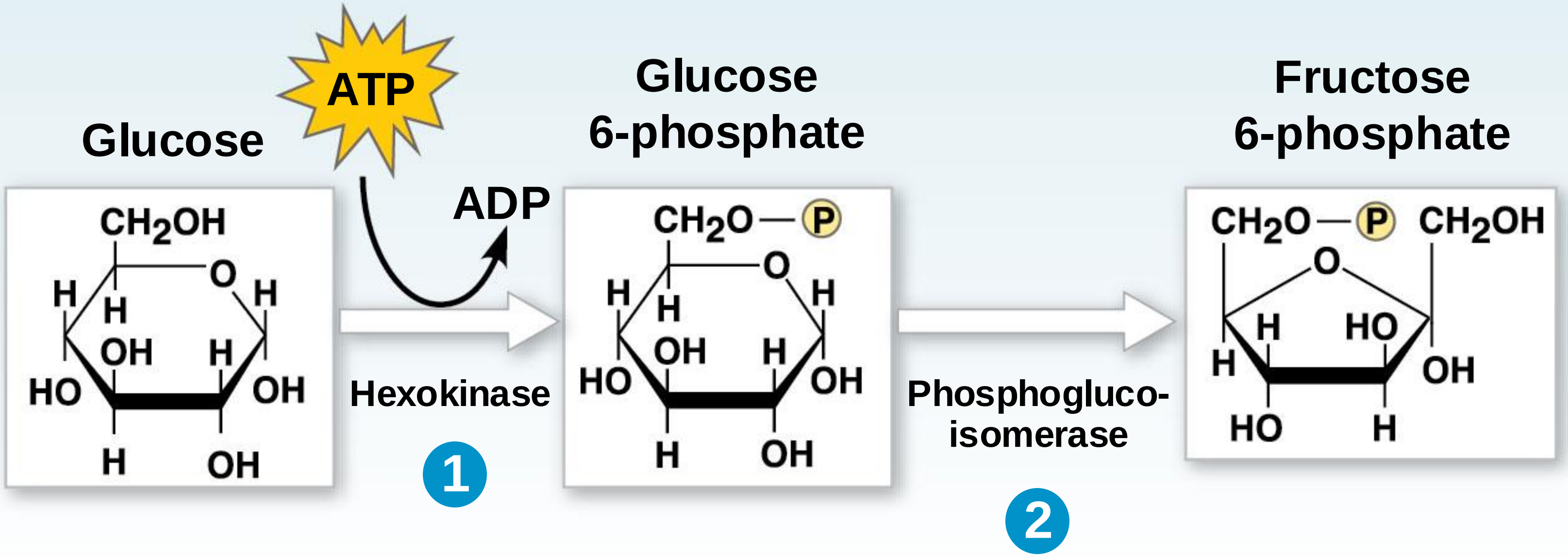
Glucose



GLYCOLYSIS: Energy Investment Phase

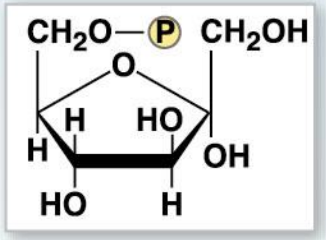


GLYCOLYSIS: Energy Investment Phase

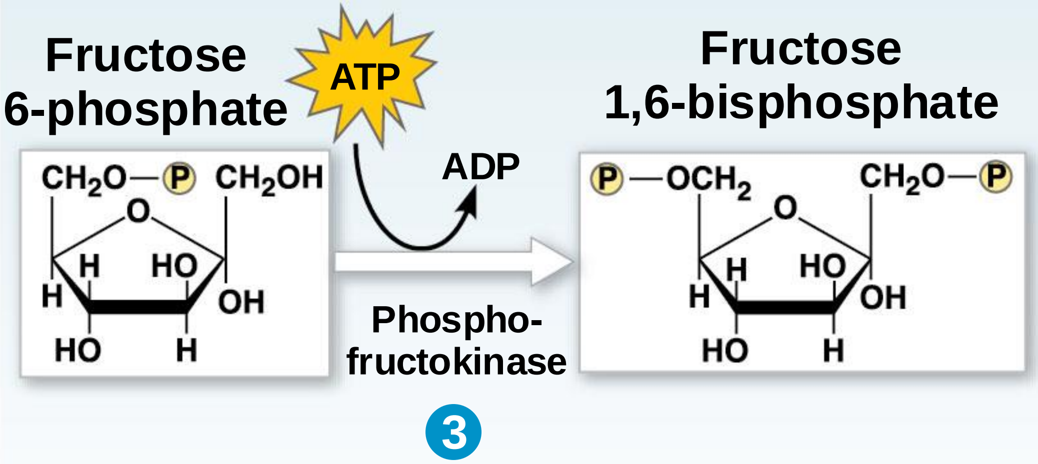


GLYCOLYSIS: Energy Investment Phase

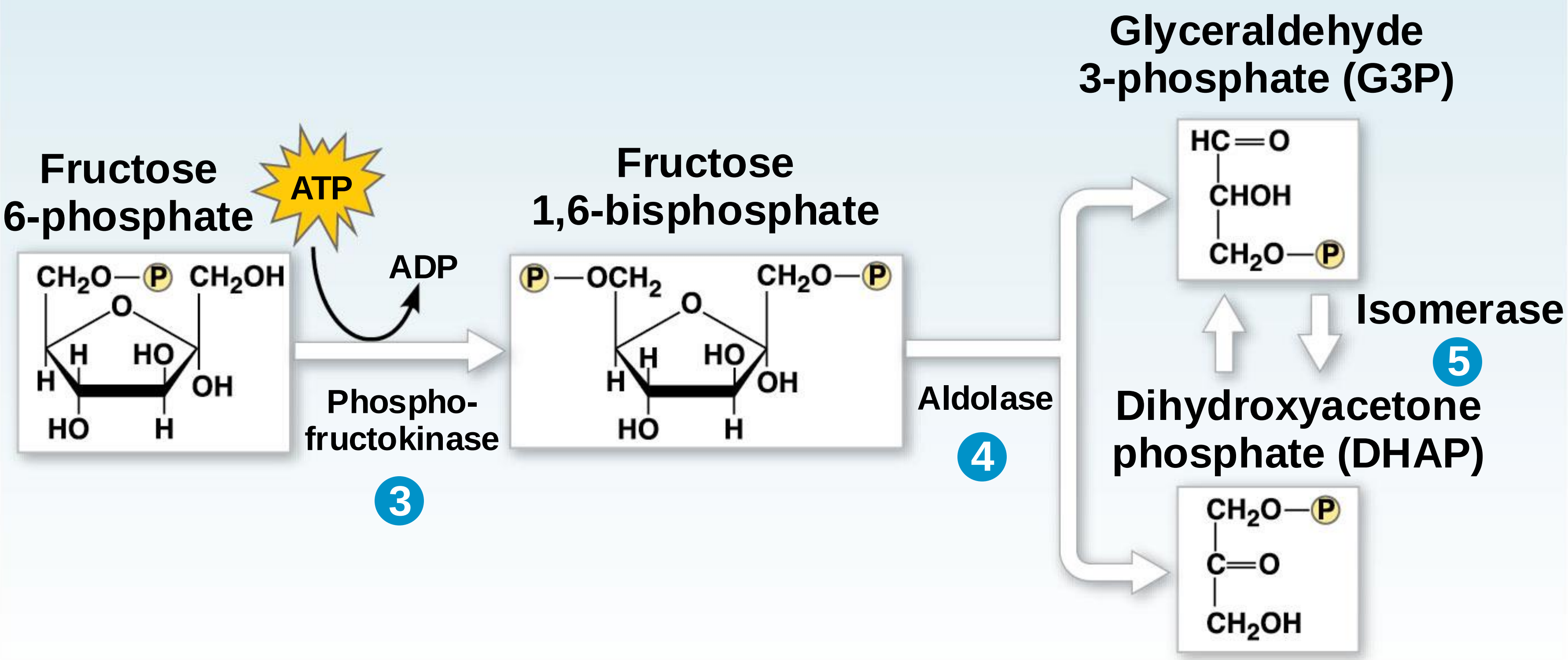
Fructose 6-phosphate



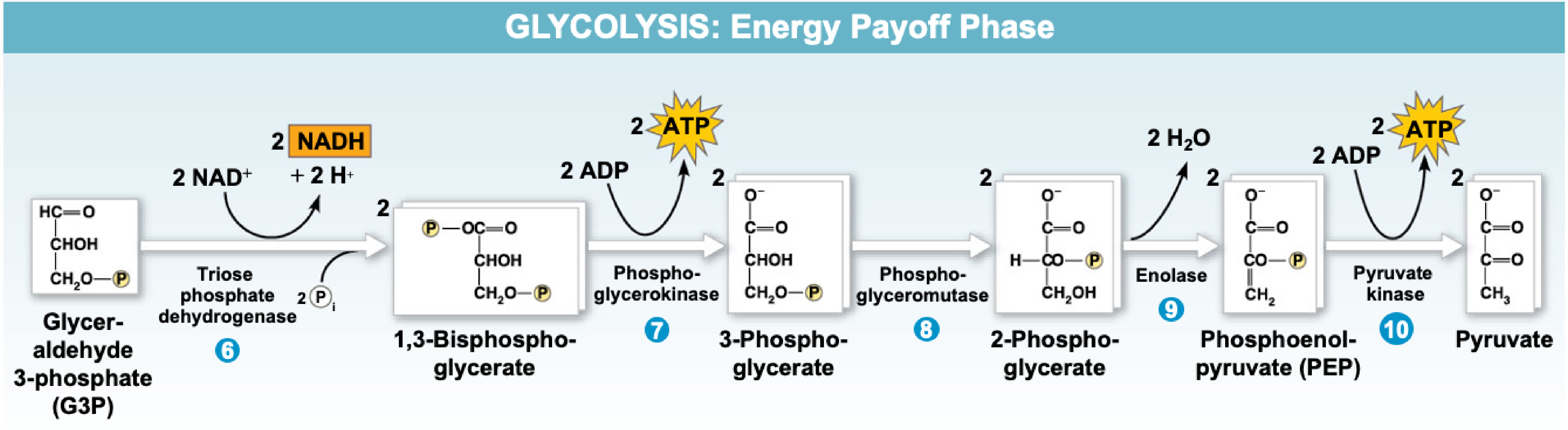
GLYCOLYSIS: Energy Investment Phase



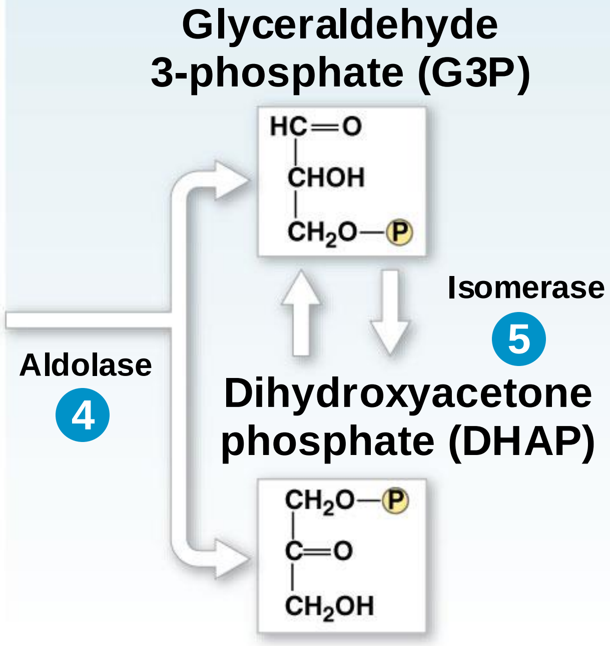
GLYCOLYSIS: Energy Investment Phase



A closer look at glycolysis (part 2: payoff phase)



GLYCOLYSIS: Energy Payoff Phase



Glyceraldehyde 3-phosphate (G3P)

Isomerase

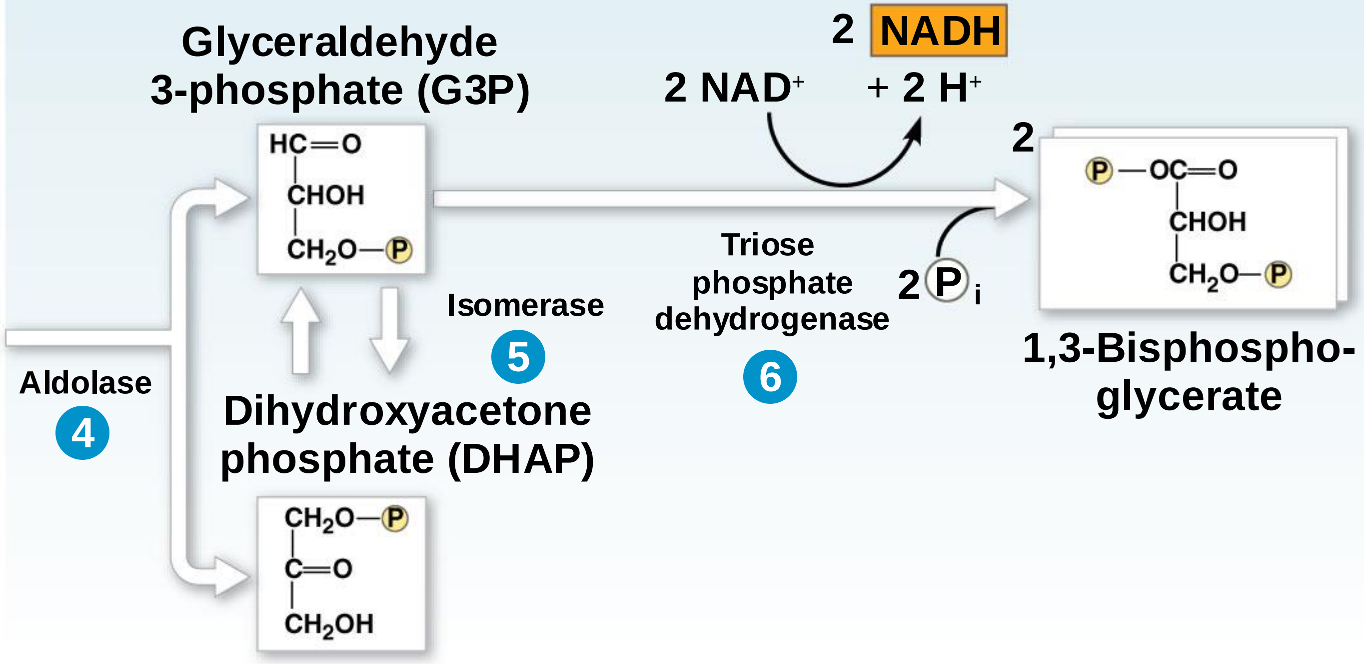
5

Aldolase

4

Dihydroxyacetone phosphate (DHAP)

GLYCOLYSIS: Energy Payoff Phase



Glyceraldehyde 3-phosphate (G3P)

HC=O
CHOH
CH_2O—P

Aldolase
④

Isomerase
⑤

Dihydroxyacetone phosphate (DHAP)

CH_2O—P
C=O
CH_2OH

2 NAD^+

2 **NADH**
+ 2 H^+

Triose phosphate dehydrogenase
⑥

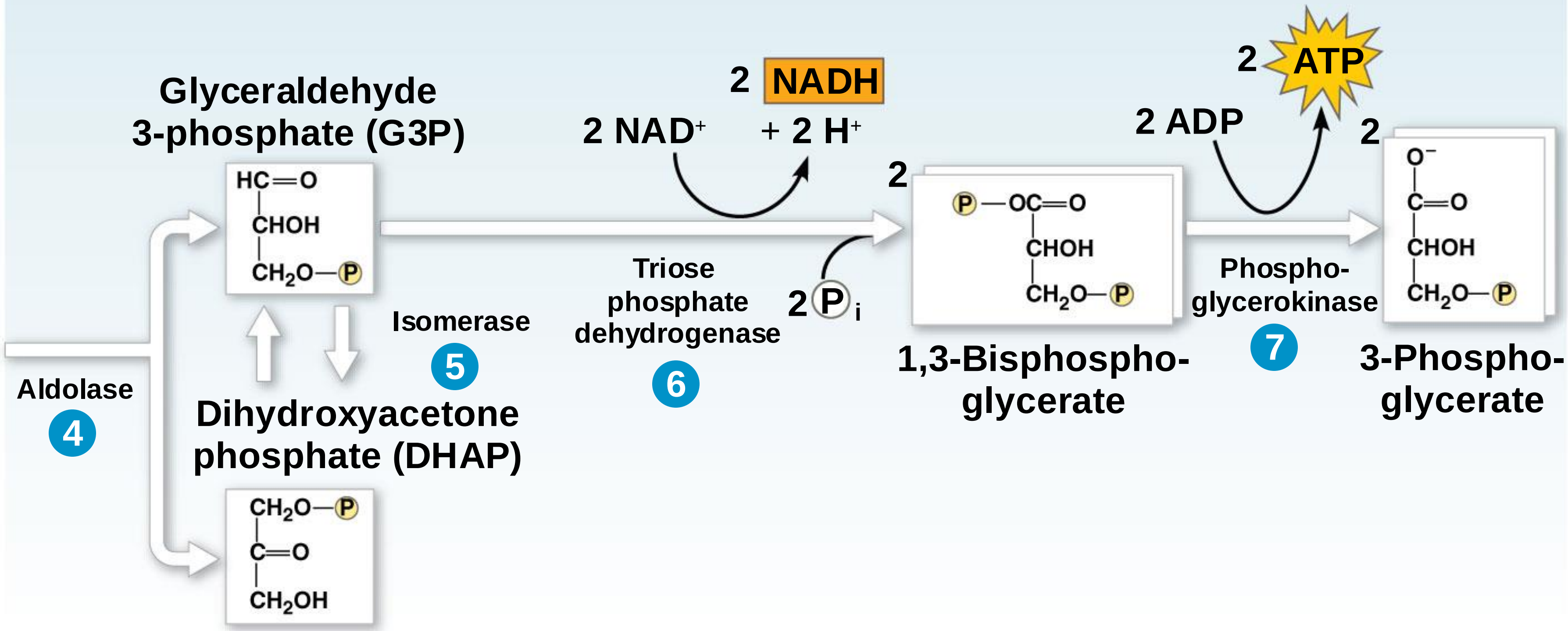
2 P_i

2

P—OC=O
CHOH
CH_2O—P

1,3-Bisphosphoglycerate

GLYCOLYSIS: Energy Payoff Phase



Aldolase ④

Glyceraldehyde 3-phosphate (G3P)

Isomerase ⑤

Dihydroxyacetone phosphate (DHAP)

2 NAD^+

2 NADH + 2 H^+

2 P_i

Triose phosphate dehydrogenase ⑥

2 1,3-Bisphosphoglycerate

2 ADP

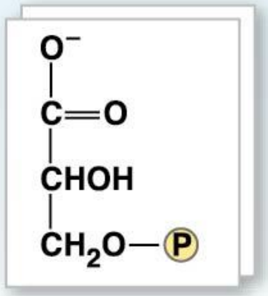
2 ATP

Phosphoglycerokinase ⑦

2 3-Phosphoglycerate

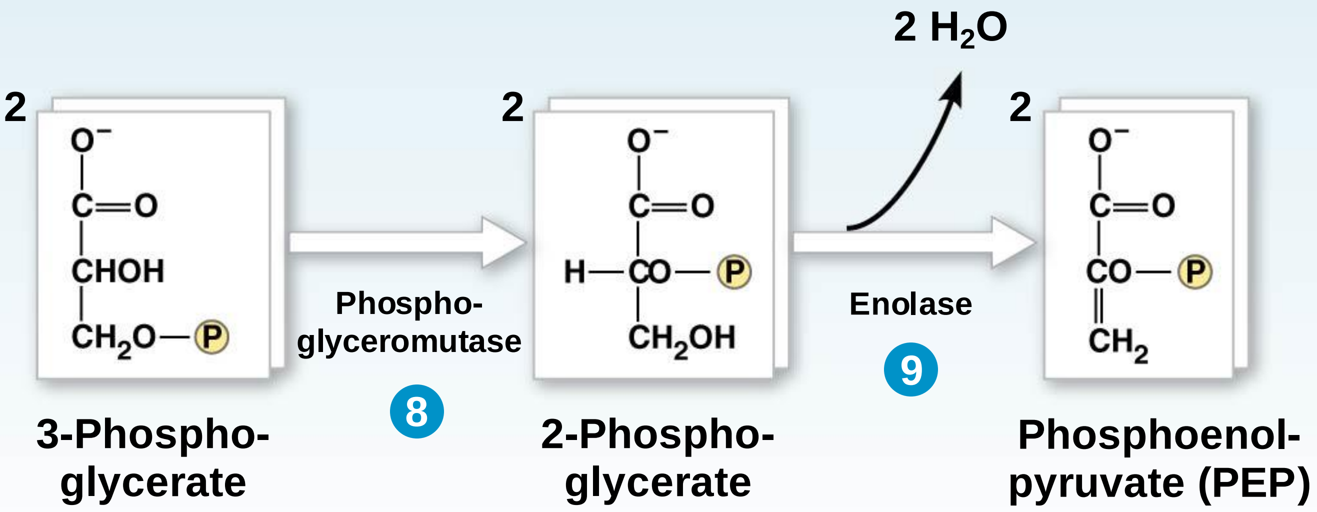
GLYCOLYSIS: Energy Payoff Phase

2



3-Phospho-glycerate

GLYCOLYSIS: Energy Payoff Phase



2 H_2O

Phospho-glyceromutase

8

Enolase

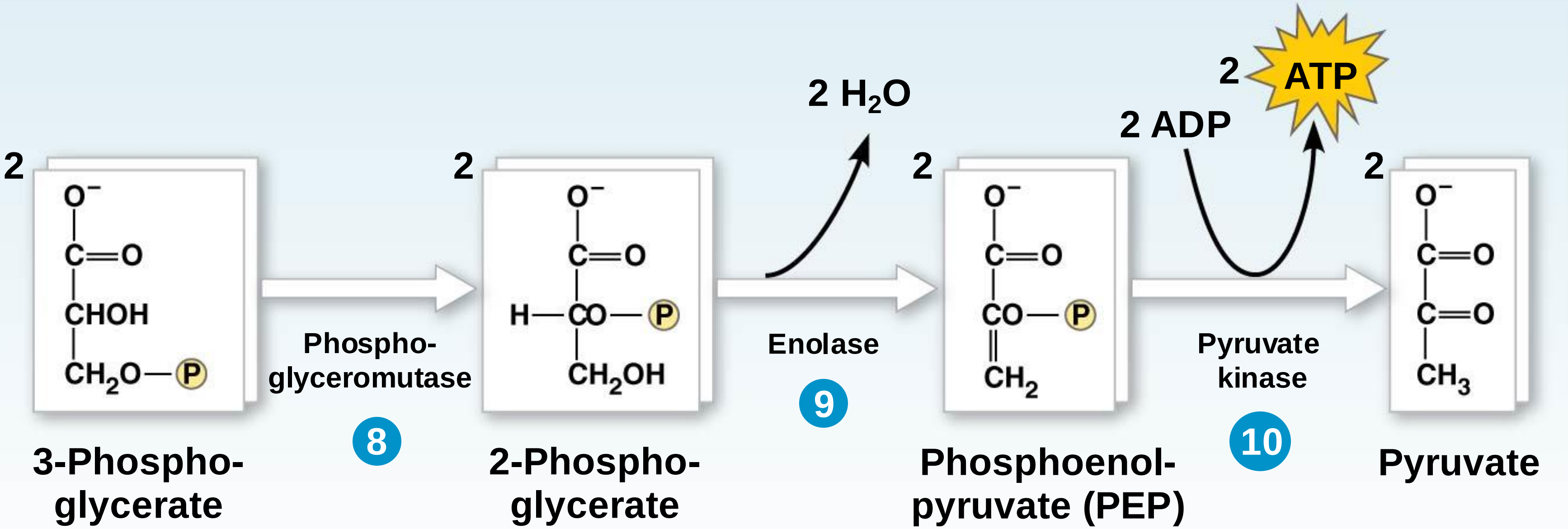
9

3-Phospho-glycerate

2-Phospho-glycerate

Phosphoenol-pyruvate (PEP)

GLYCOLYSIS: Energy Payoff Phase



3-Phosphoglycerate

Phosphoglyceromutase

8

2-Phosphoglycerate

Enolase

9

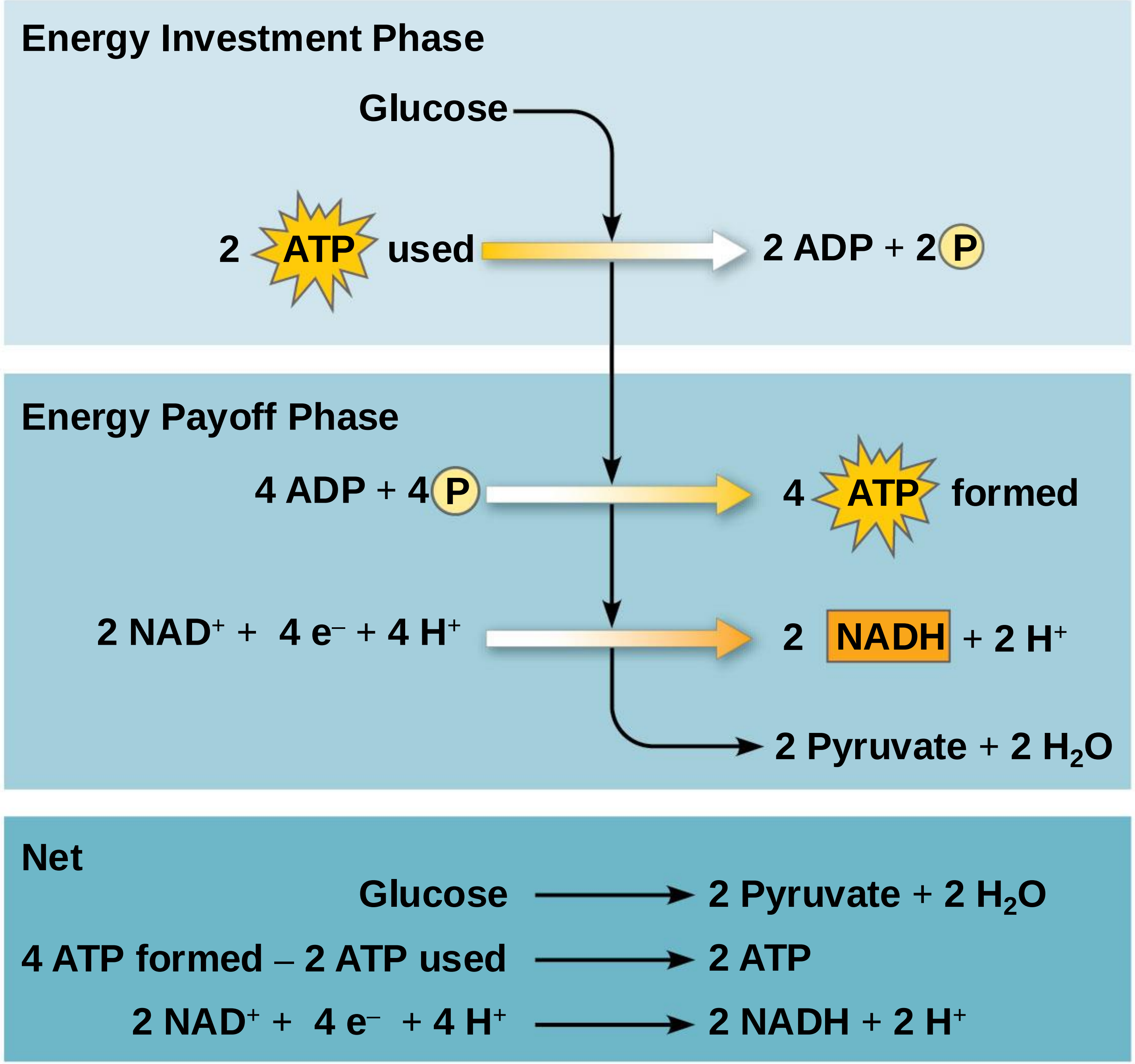
Phosphoenolpyruvate (PEP)

Pyruvate kinase

10

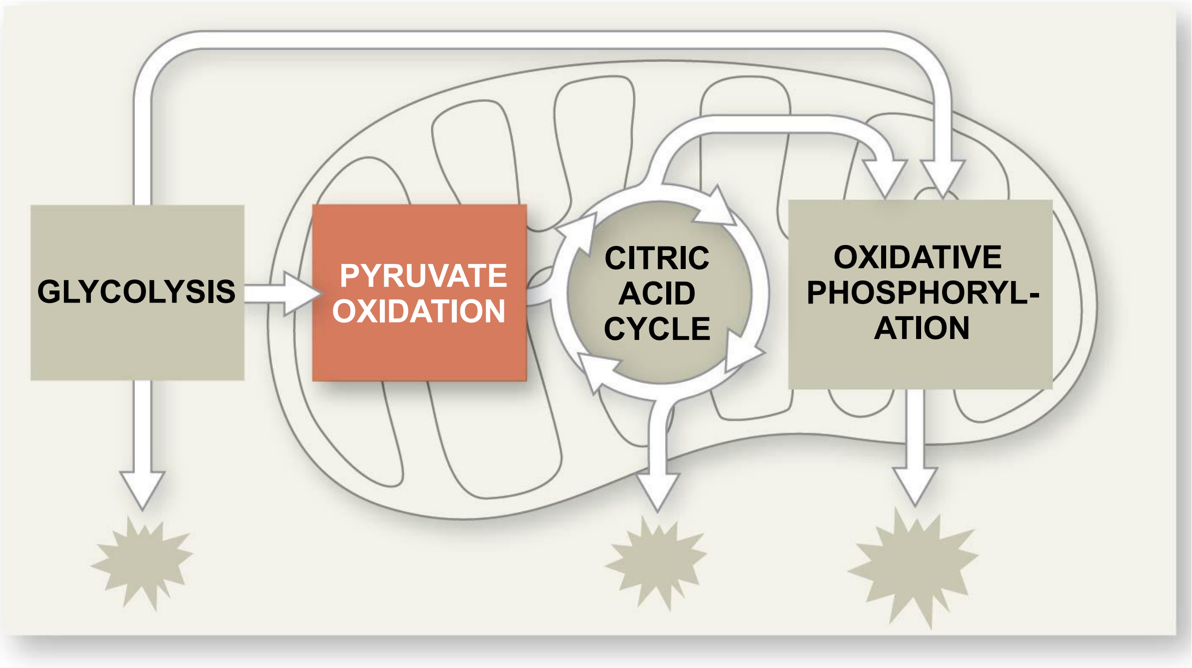
Pyruvate

The energy input and output of glycolysis: overview



After pyruvate is oxidized, the citric acid cycle or Krebs cycle completes the energy-yielding oxidation of organic molecules

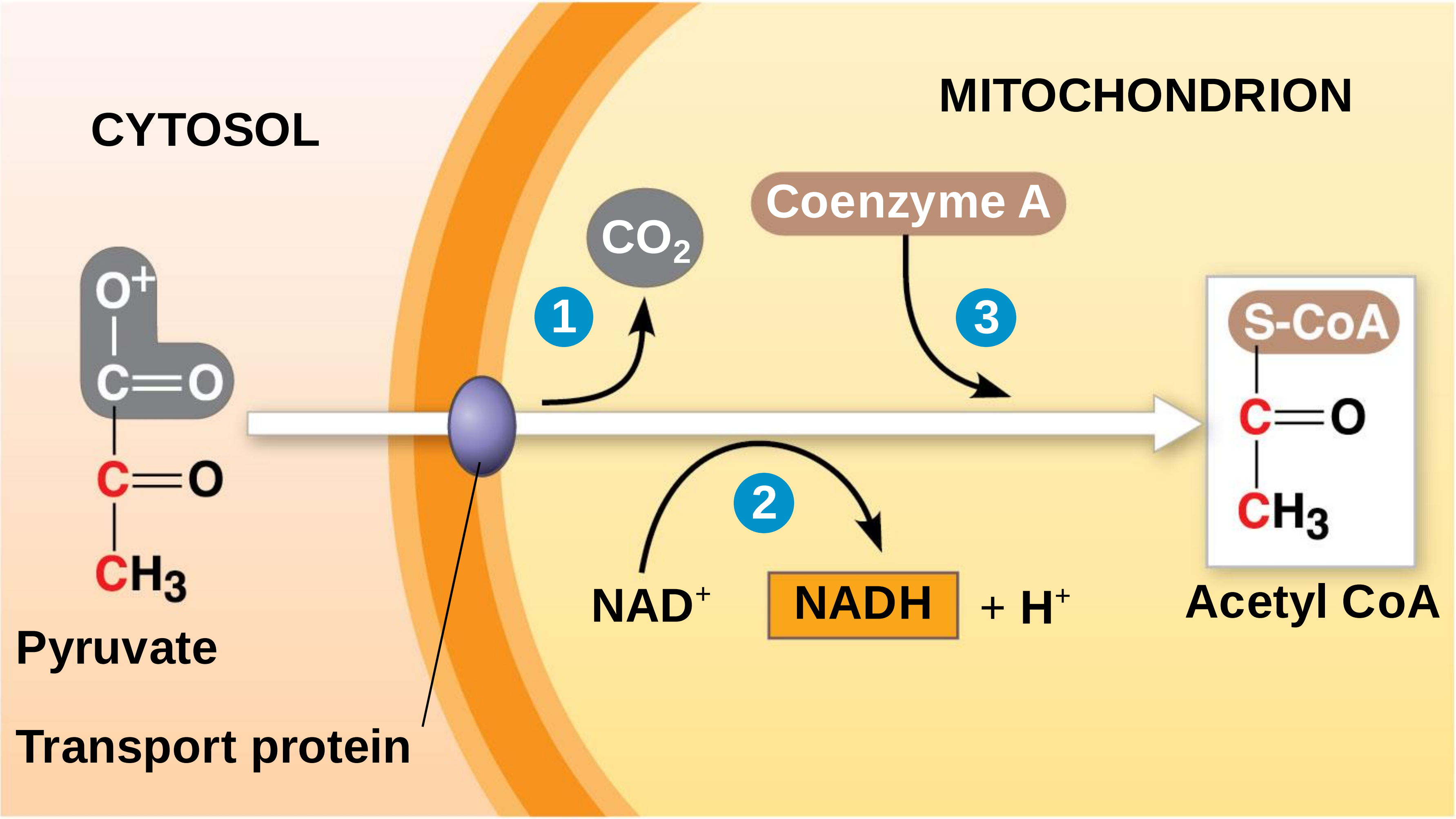
- In the presence of O_2, pyruvate enters a mitochondrion (in eukaryotic cells), where the oxidation of glucose is completed



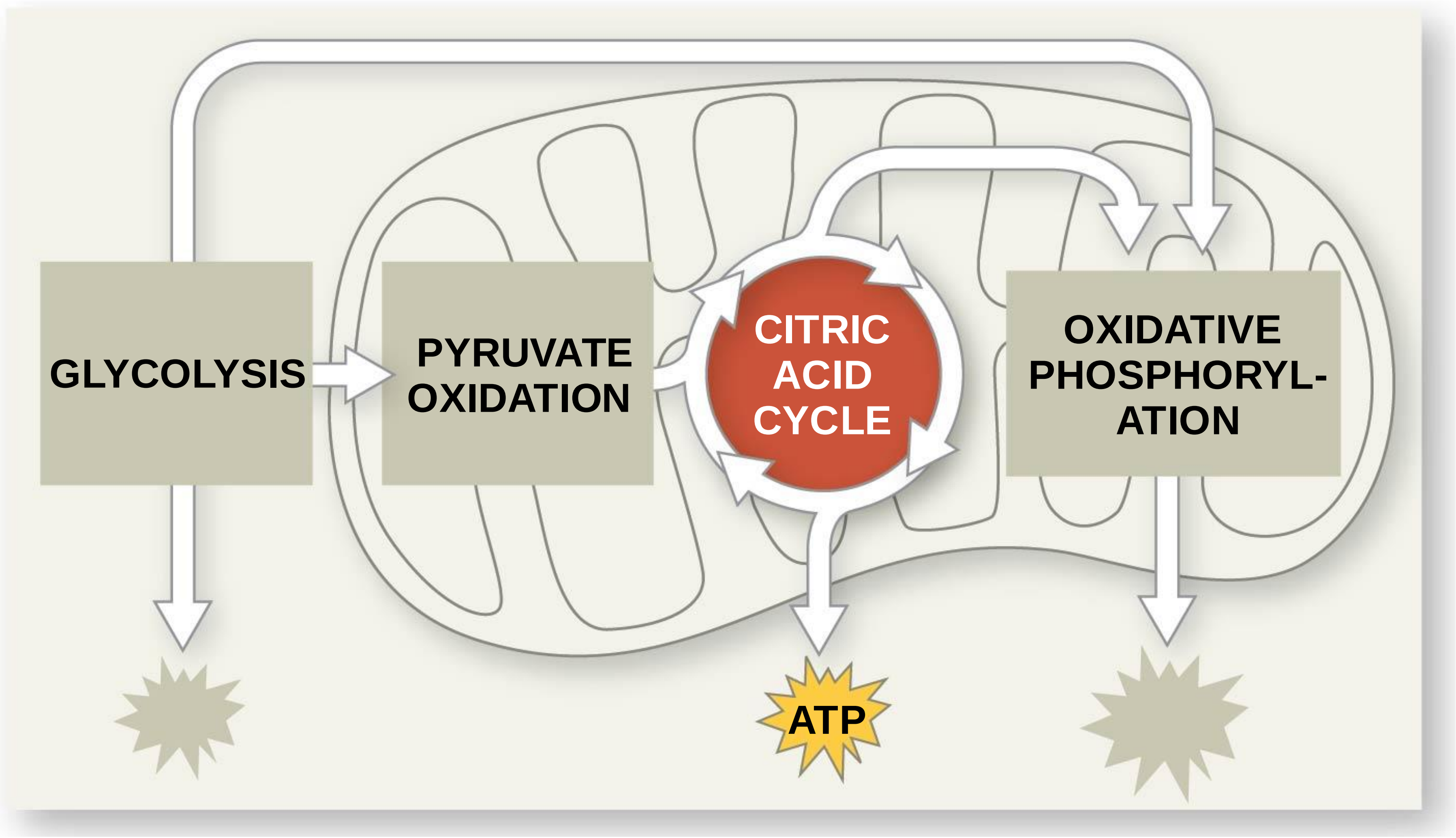
Oxidation of Pyruvate to Acetyl CoA

- Before the citric acid cycle can begin, pyruvate must be converted to acetyl coenzyme A (**acetyl CoA**), which links glycolysis to the citric acid cycle
- This step is carried out by a multienzyme complex that catalyzes three reactions
  1. Oxidation of pyruvate and release of CO_2
  2. Reduction of NAD^+ to NADH
  3. Combination of the remaining two-carbon fragment and coenzyme A to form acetyl CoA

Oxidation of Pyruvate to Acetyl CoA



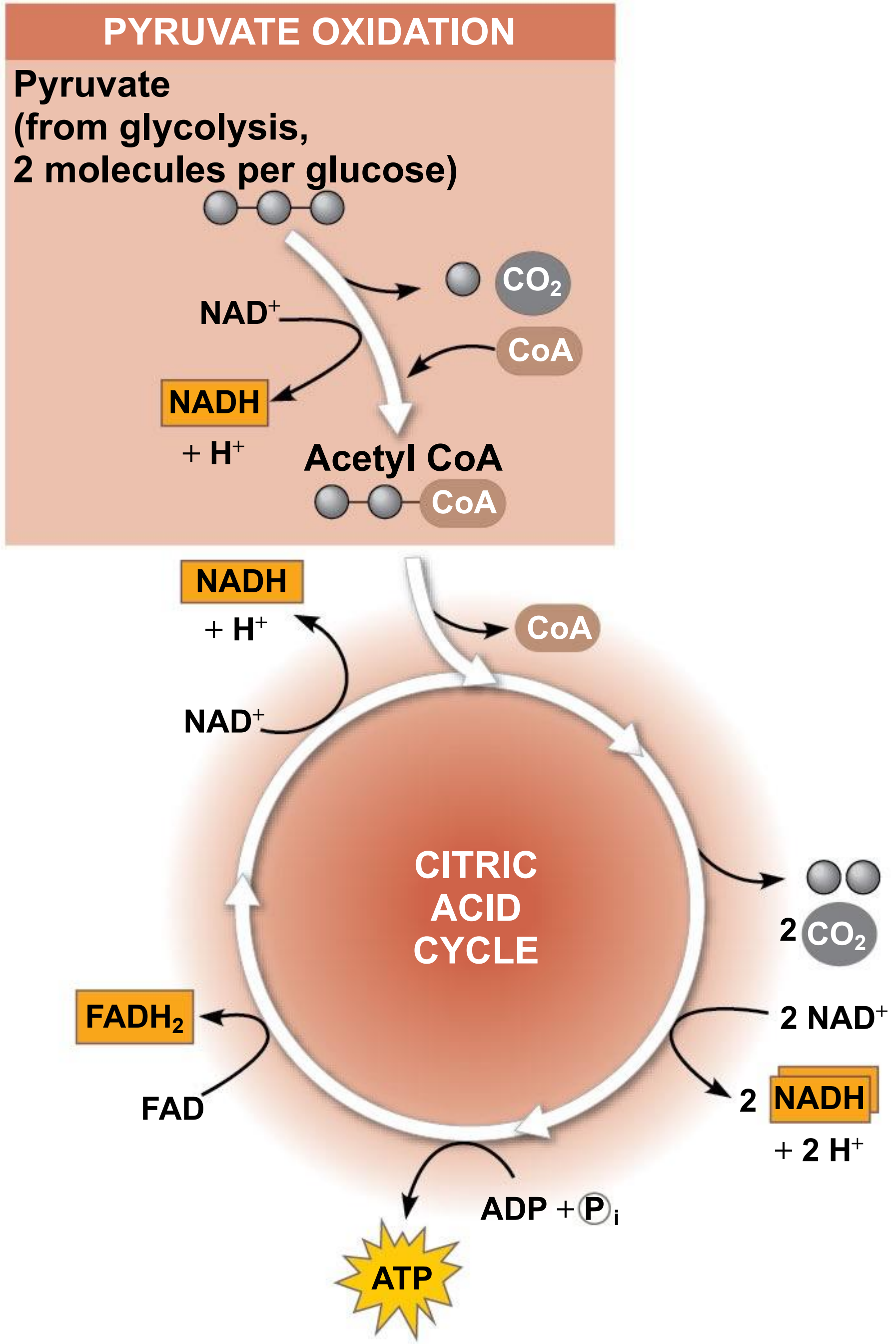
Zooming into the
cellular respiration: citric acid cycle

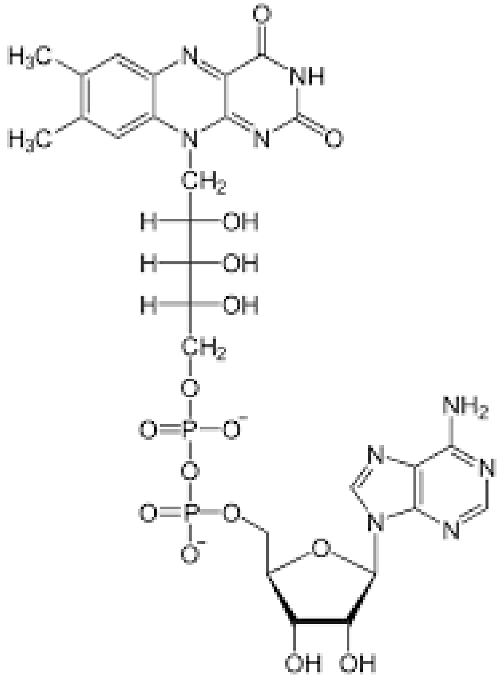

GLYCOLYSIS
PYRUVATE OXIDATION
CITRIC ACID CYCLE
OXIDATIVE PHOSPHORYL- ATION
ATP

The Citric Acid Cycle

- The citric acid cycle, also called the Krebs cycle, completes the breakdown of pyruvate to CO_2
- The cycle oxidizes organic fuel derived from pyruvate, generating 1 ATP, 3 NADH, and 1 $FADH_2$ per turn

$FADH_2$/FAD+ is another coenzyme which carries electrons during the Krebs cycle.



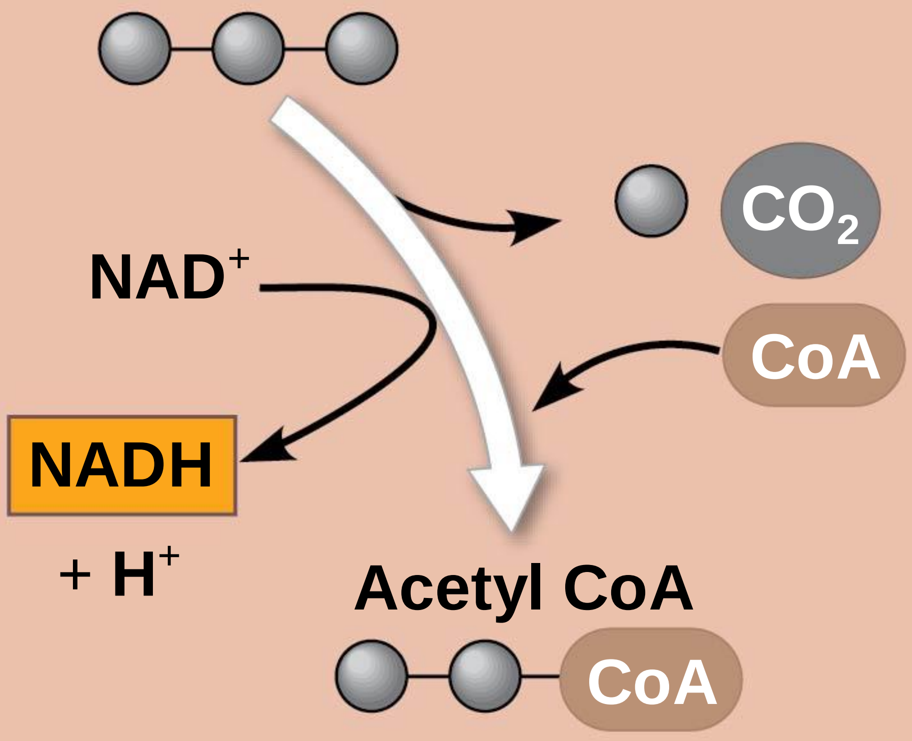


Flavine adenine dinucleotide (FAD)

- The citric acid cycle has eight steps, each catalyzed by a specific enzyme
- The acetyl group of acetyl CoA joins the cycle by combining with oxaloacetate, forming **citrate** (1st step of the cycle)
- The next seven steps decompose the citrate back to oxaloacetate, making the process a cycle
- The NADH and $FADH_2$ produced by the cycle relay electrons extracted from food to the electron transport chain

PYRUVATE OXIDATION

Pyruvate
(from glycolysis,
2 molecules per glucose)



CO_2

NAD^+

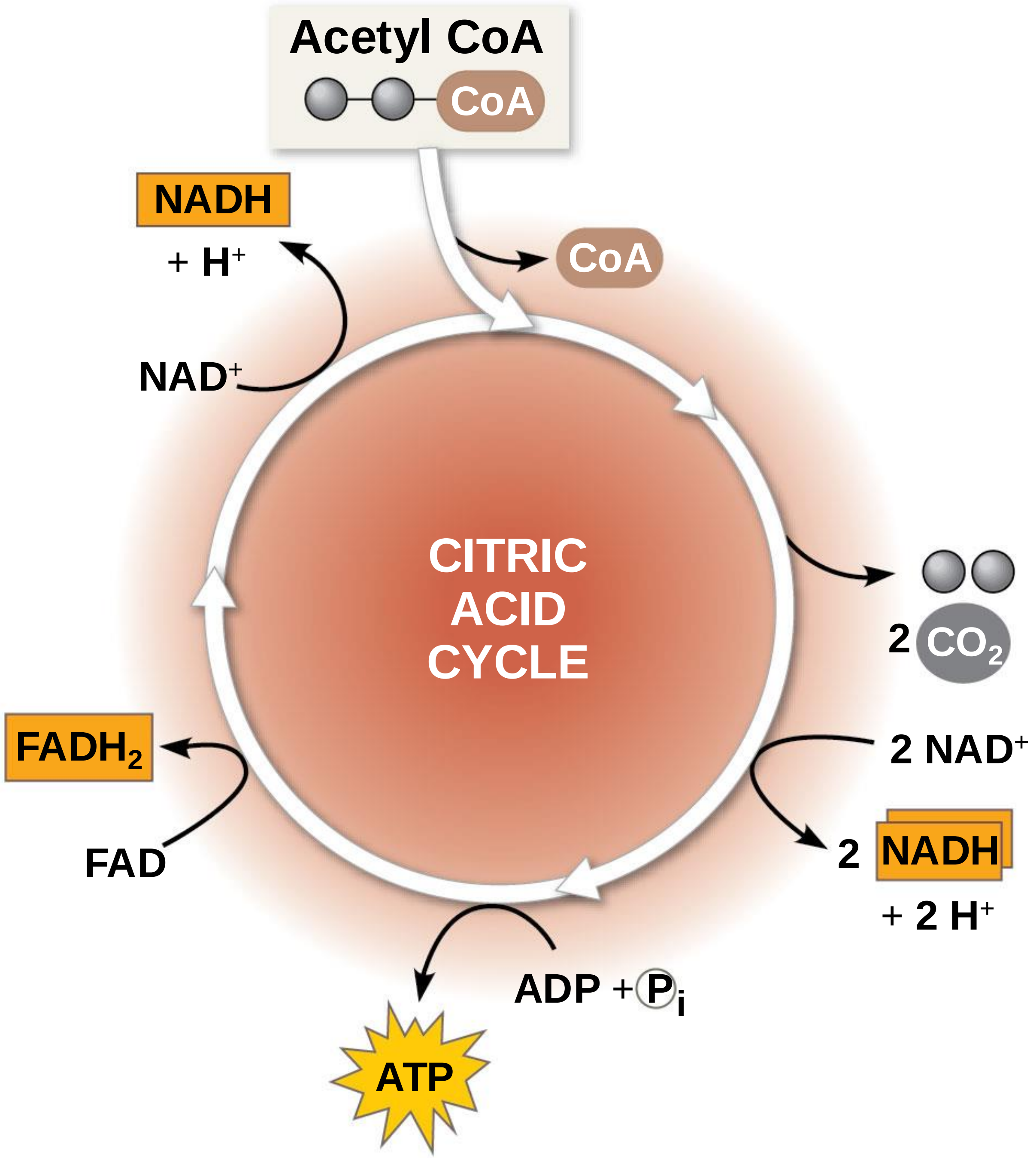
CoA

NADH

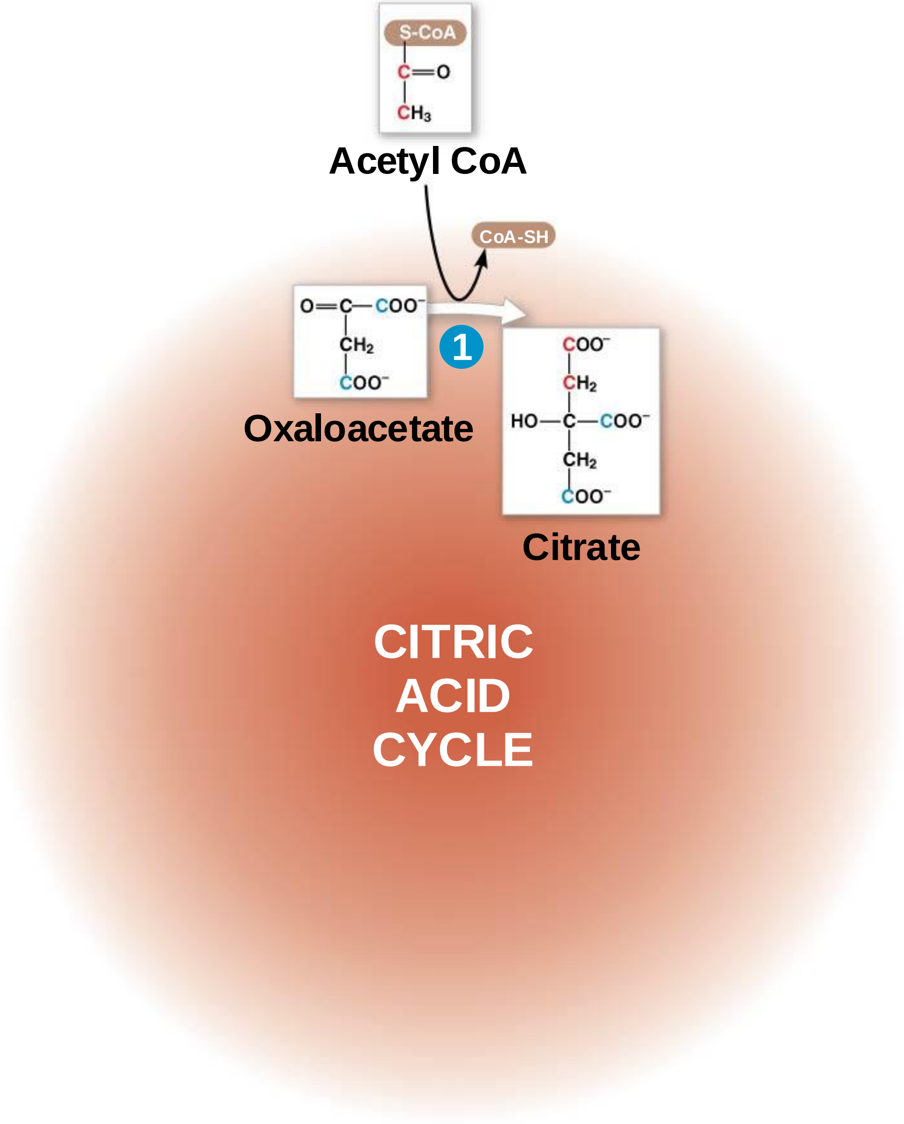
$+ H^+$

Acetyl CoA

CoA



Acetyl CoA
CoA
NADH
+ H+
NAD+
CoA
CITRIC ACID CYCLE
2 CO2
2 NAD+
2 NADH
+ 2 H+
FADH2
FAD
ADP + Pi
ATP

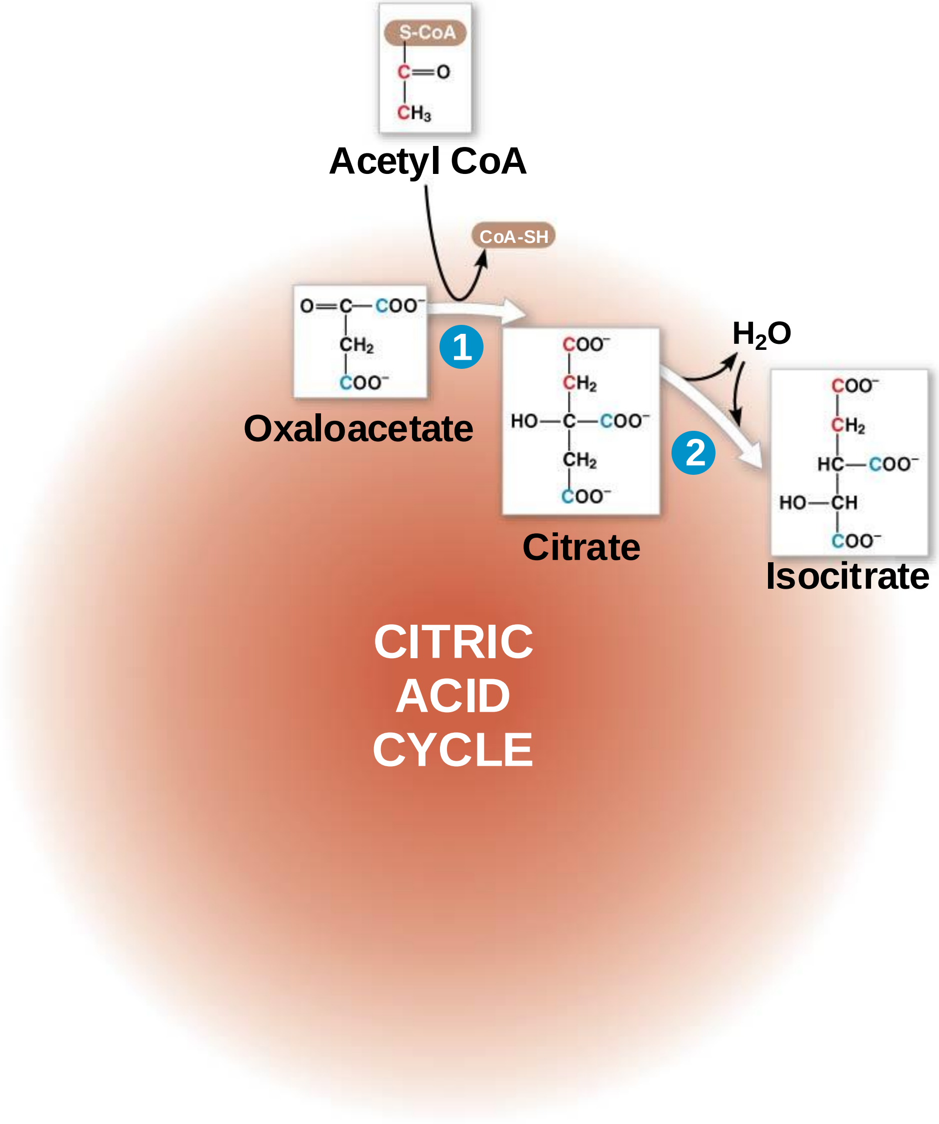


Acetyl CoA

Oxaloacetate

Citrate

CITRIC ACID CYCLE



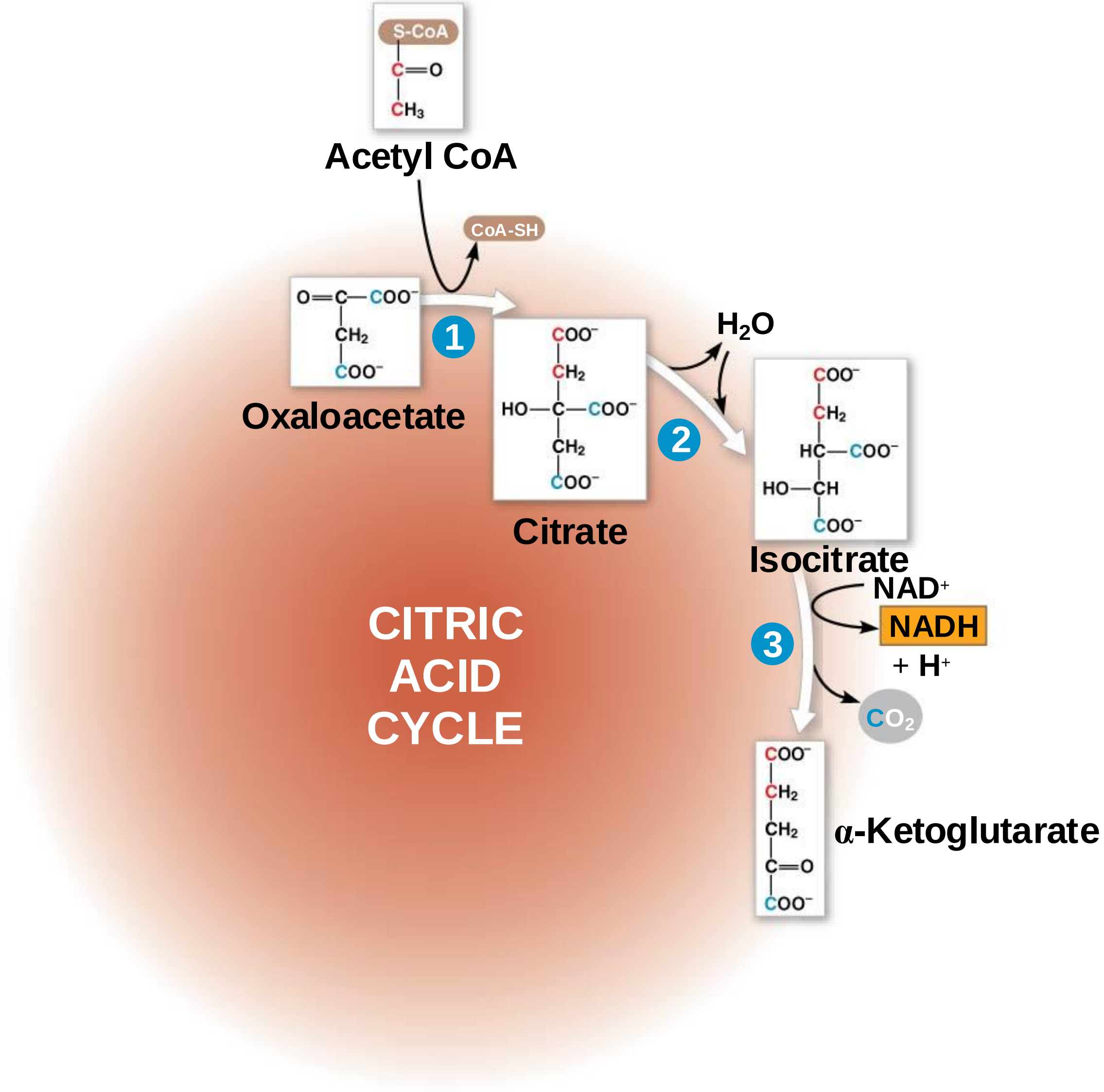
Acetyl CoA

Oxaloacetate

Citrate

Isocitrate

CITRIC
ACID
CYCLE



Acetyl CoA

CoA-SH

Oxaloacetate

1

Citrate

H_2O

2

Isocitrate

NAD^+

NADH

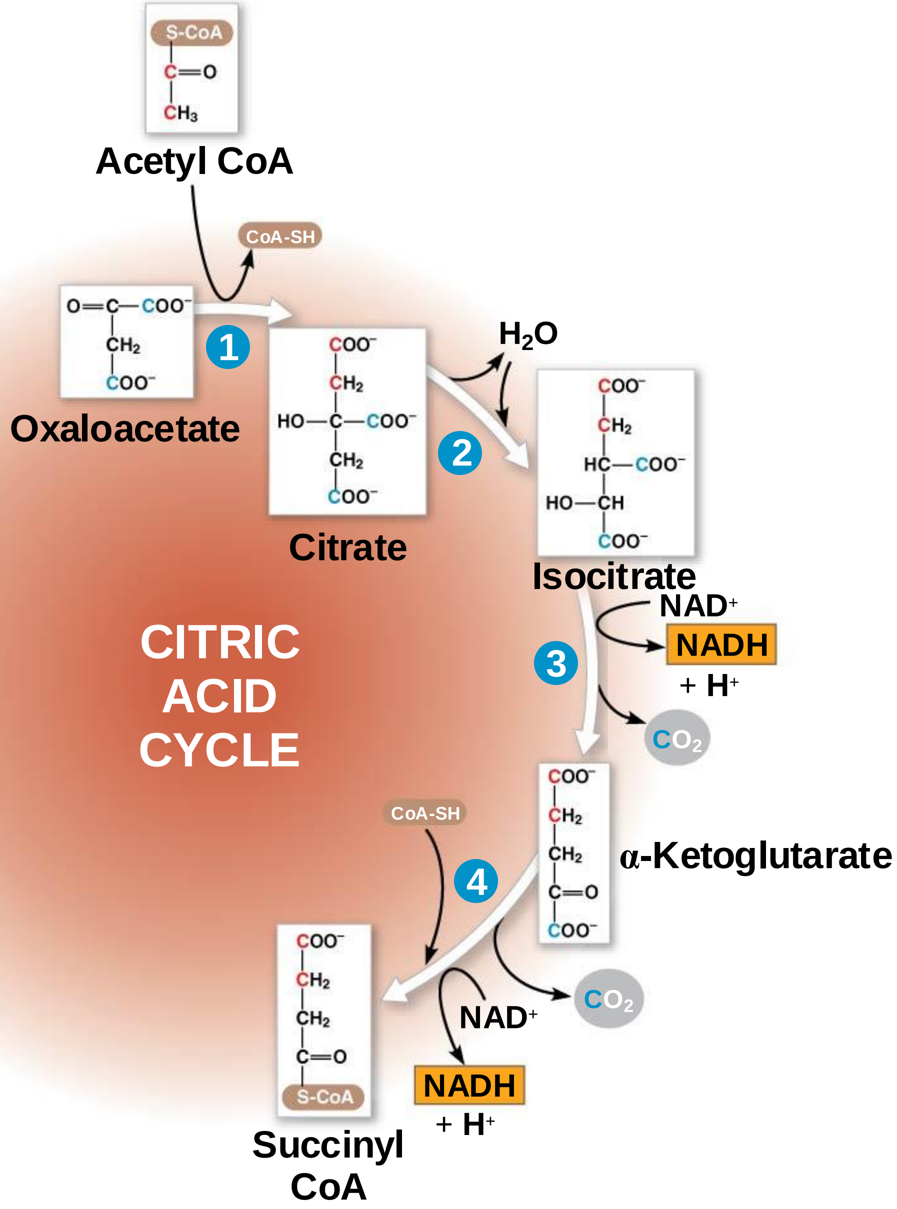
$+ H^+$

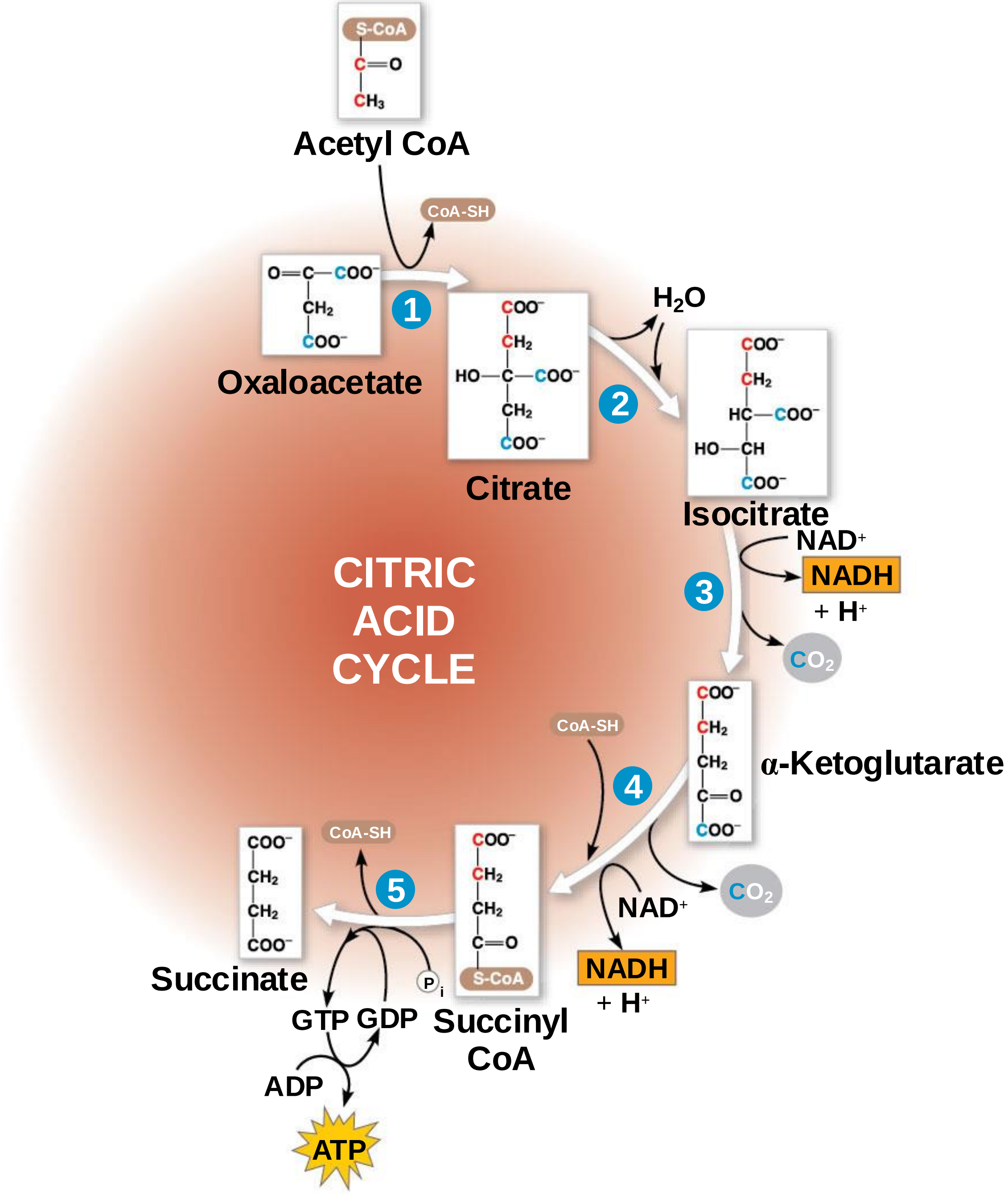
3

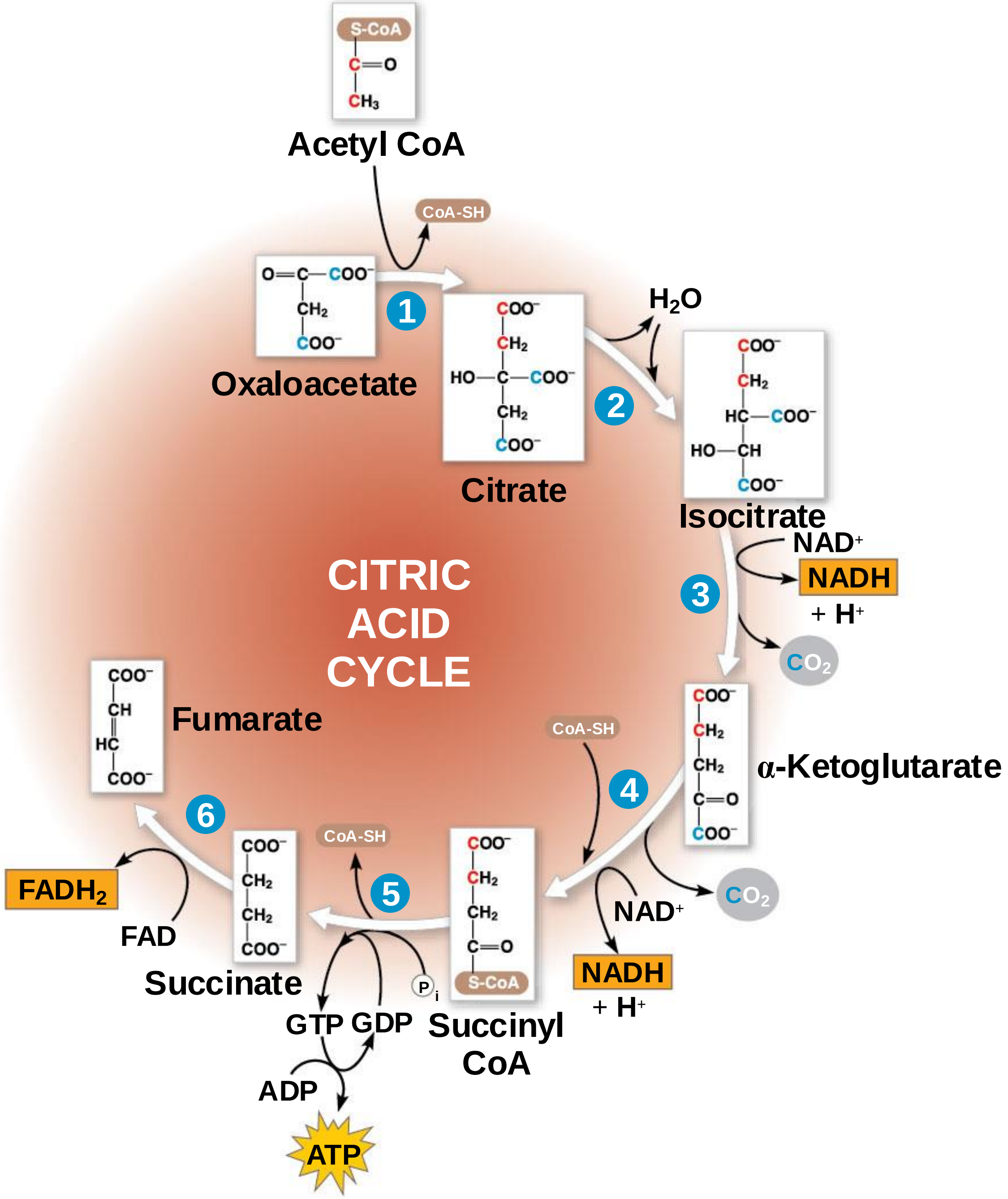
CO_2

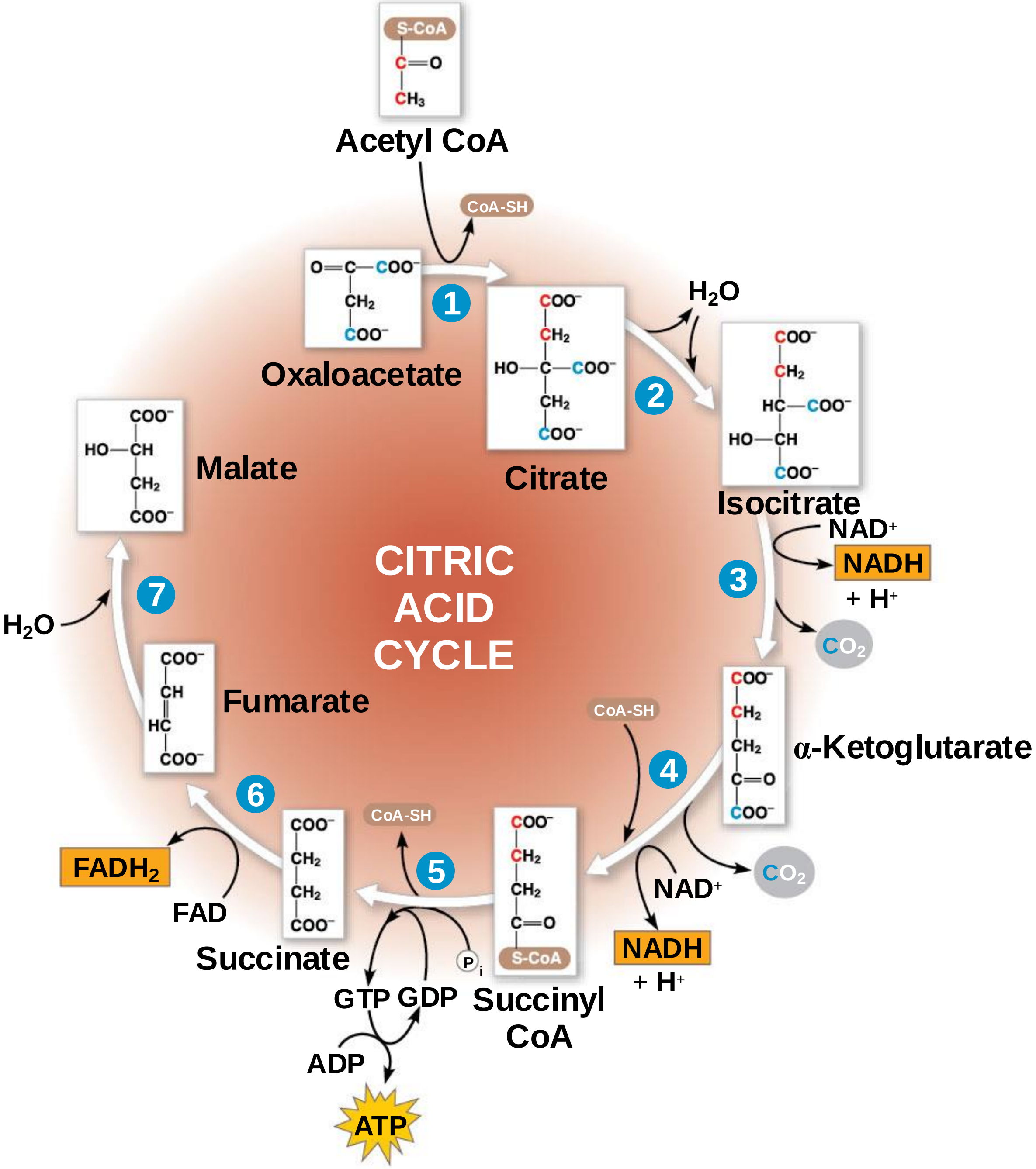
α-Ketoglutarate

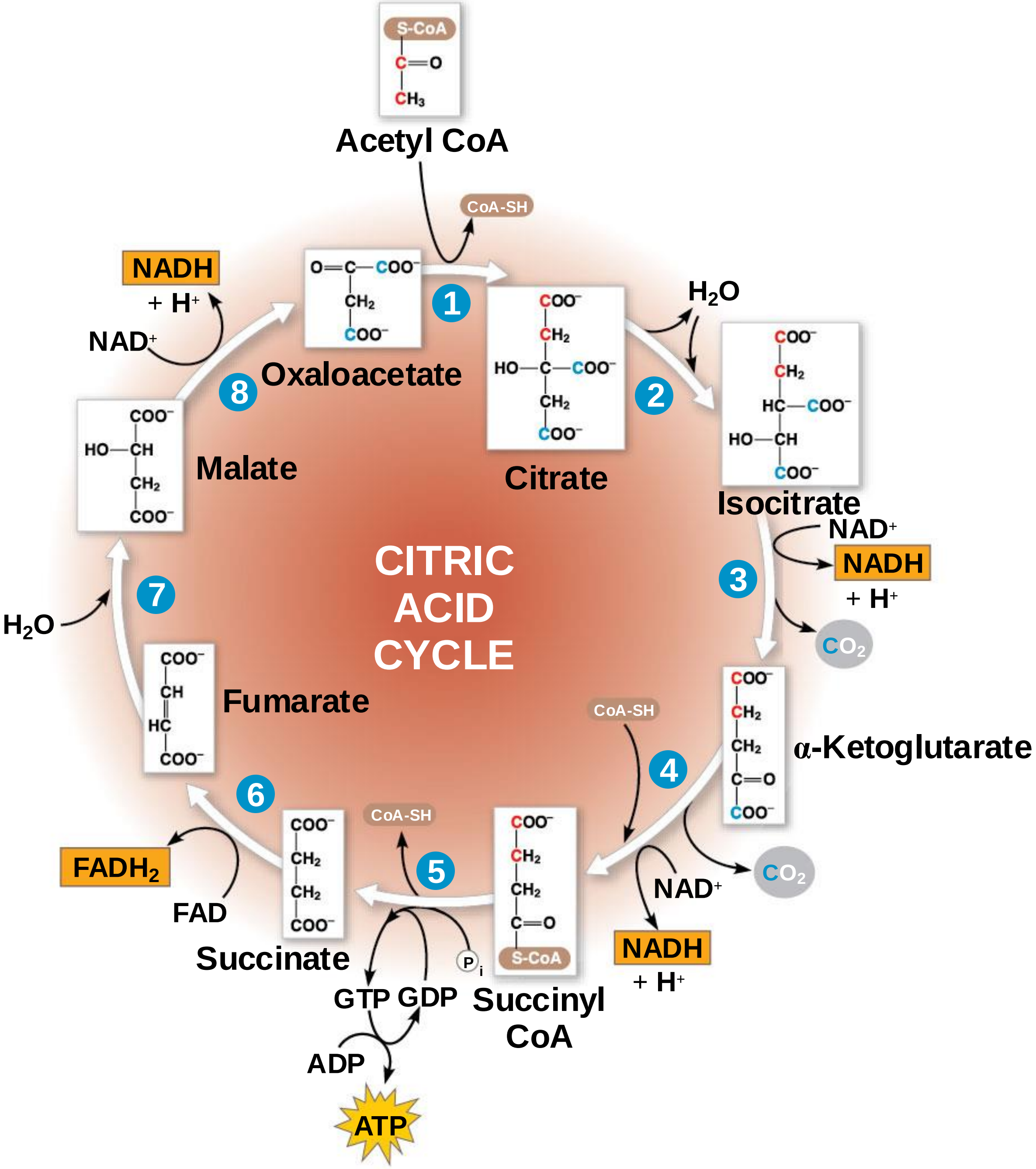
CITRIC ACID CYCLE


S-CoA
C=O
CH3
Acetyl CoA
CoA-SH
O=C—COO⁻
CH2
COO⁻
Oxaloacetate
1
COO⁻
CH2
HO—C—COO⁻
CH2
COO⁻
Citrate
H2O
2
COO⁻
CH2
HC—COO⁻
HO—CH
COO⁻
Isocitrate
NAD+
NADH
+ H+
3
CO2
CITRIC
ACID
CYCLE
COO⁻
CH2
CH2
C=O
COO⁻
α-Ketoglutarate
CoA-SH
4
CO2
NAD+
NADH
+ H+
COO⁻
CH2
CH2
C=O
S-CoA
Succinyl
CoA

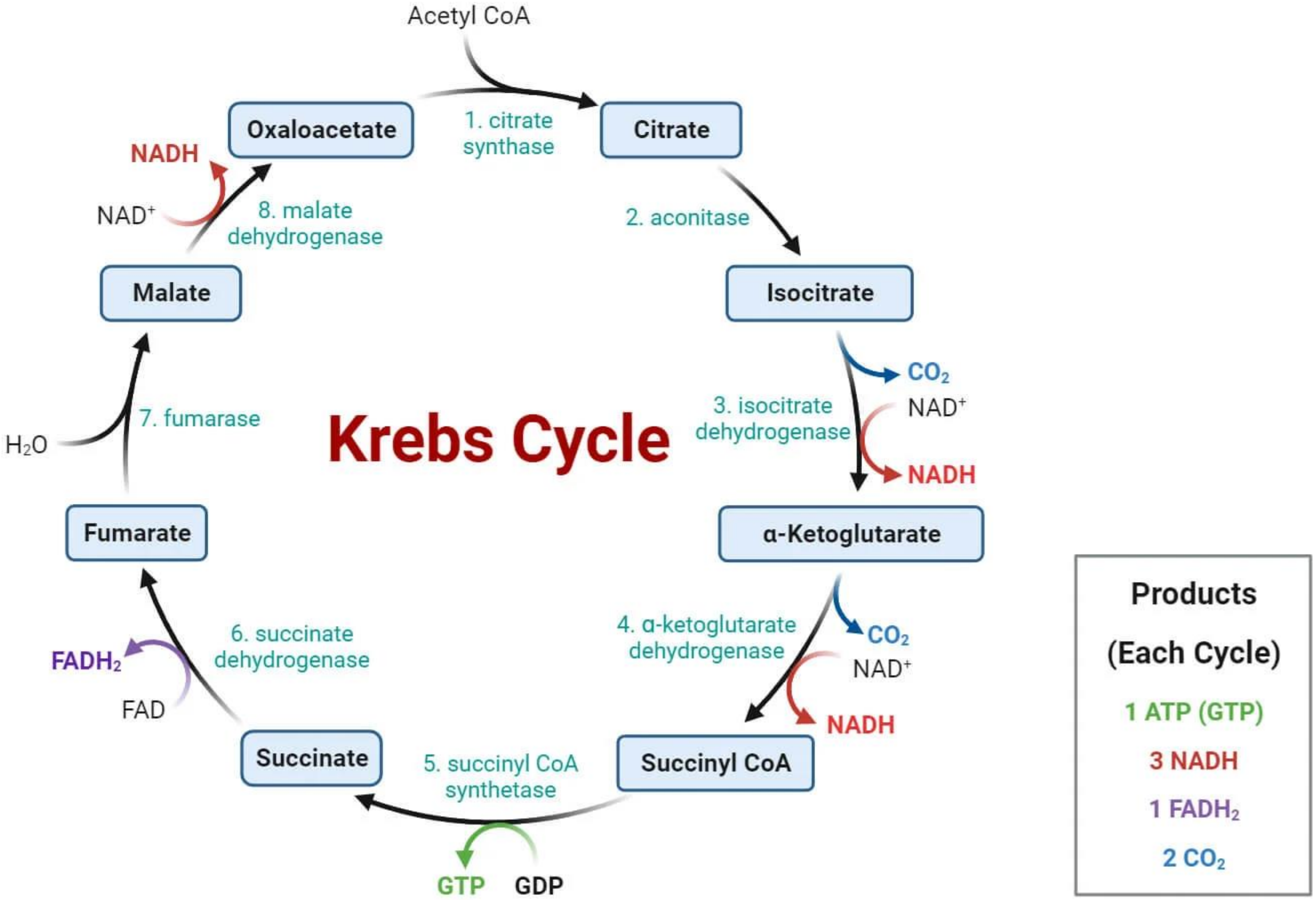

Acetyl CoA
S-CoA
C=O
CH3
CoA-SH
1
Oxaloacetate
Citrate
H2O
2
Isocitrate
NAD+
NADH
+ H+
3
CO2
α-Ketoglutarate
CoA-SH
4
CO2
NAD+
NADH
+ H+
Succinyl CoA
CoA-SH
5
Pi
Succinate
GTP
GDP
ADP
ATP
CITRIC ACID CYCLE


Acetyl CoA
S-CoA
CoA-SH
Oxaloacetate
1
Citrate
H2O
2
Isocitrate
NAD+
NADH
+ H+
3
CO2
α-Ketoglutarate
CoA-SH
4
CO2
NAD+
NADH
+ H+
Succinyl CoA
S-CoA
CoA-SH
5
Pi
GTP
GDP
ADP
ATP
Succinate
FAD
FADH2
6
Fumarate
CITRIC ACID CYCLE

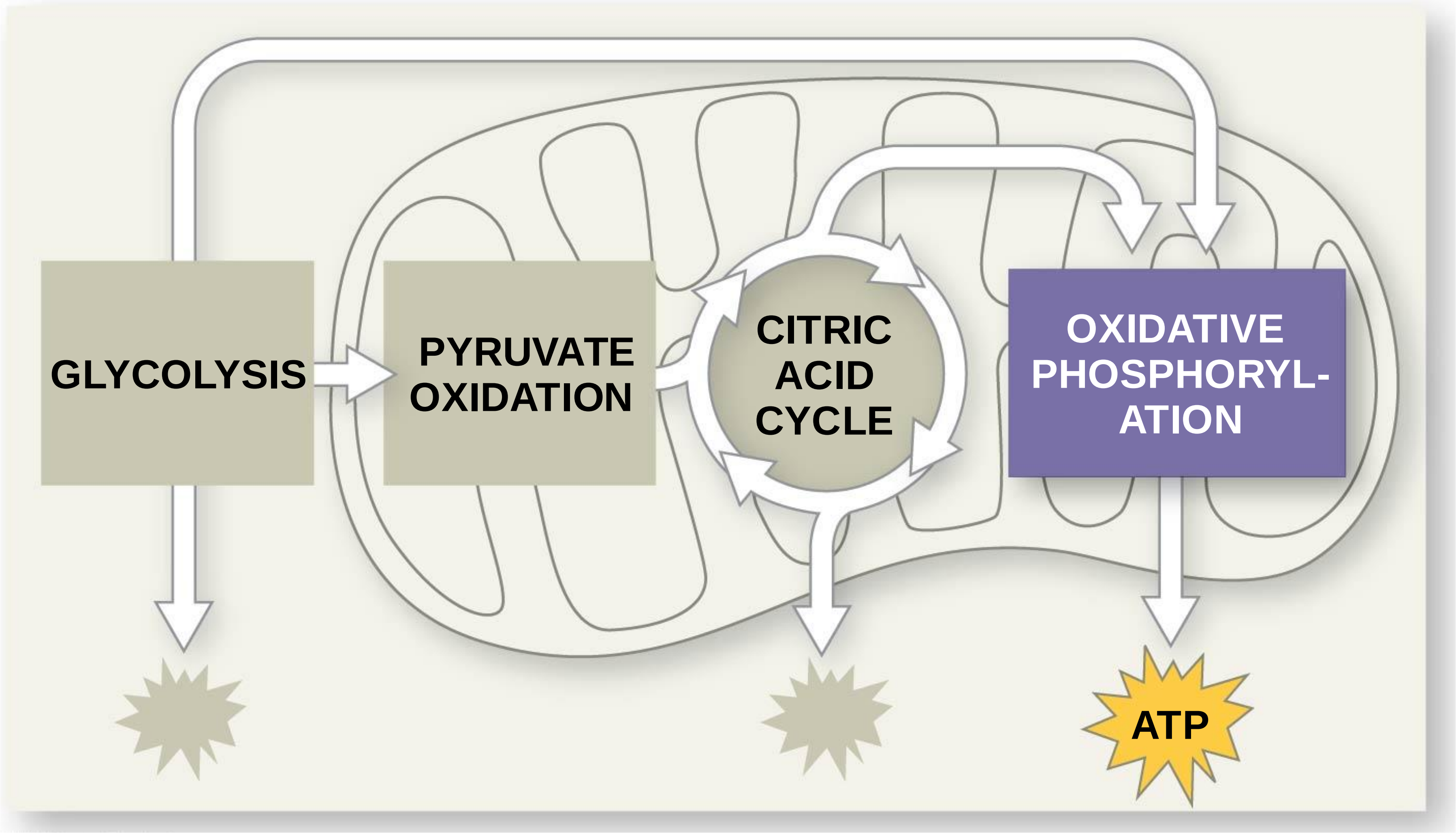

Acetyl CoA
S-CoA
CoA-SH
CITRIC
ACID
CYCLE
1
Oxaloacetate
Citrate
2
H_2O
Isocitrate
3
NAD^+
NADH
+ H^+
CO_2
α-Ketoglutarate
4
CoA-SH
NAD^+
NADH
+ H^+
CO_2
Succinyl
CoA
5
CoA-SH
P_i
GTP
GDP
ADP
ATP
Succinate
6
FAD
$FADH_2$
Fumarate
7
H_2O
Malate


Acetyl CoA
S-CoA
C=O
CH3
CoA-SH
1
Oxaloacetate
Citrate
H2O
2
Isocitrate
NAD+
NADH
+ H+
3
CO2
α-Ketoglutarate
CoA-SH
4
CO2
NAD+
NADH
+ H+
Succinyl CoA
S-CoA
CoA-SH
5
Pi
GTP
GDP
ADP
ATP
Succinate
6
FADH2
FAD
Fumarate
7
H2O
Malate
8
NAD+
NADH
+ H+
CITRIC ACID CYCLE

The enzymes


Acetyl CoA
Oxaloacetate
1. citrate synthase
Citrate
2. aconitase
Isocitrate
CO_2
3. isocitrate dehydrogenase
NAD^+
NADH
α-Ketoglutarate
4. α-ketoglutarate dehydrogenase
CO_2
NAD^+
NADH
Succinyl CoA
5. succinyl CoA synthetase
GTP
GDP
Succinate
6. succinate dehydrogenase
$FADH_2$
FAD
Fumarate
7. fumarase
H_2O
Malate
8. malate dehydrogenase
NAD^+
NADH
Krebs Cycle
Products
(Each Cycle)
1 ATP (GTP)
3 NADH
1 $FADH_2$
2 CO_2

Zooming into the cellular respiration: oxidative phosphorilation


GLYCOLYSIS
PYRUVATE OXIDATION
CITRIC ACID CYCLE
OXIDATIVE PHOSPHORYL-ATION
ATP

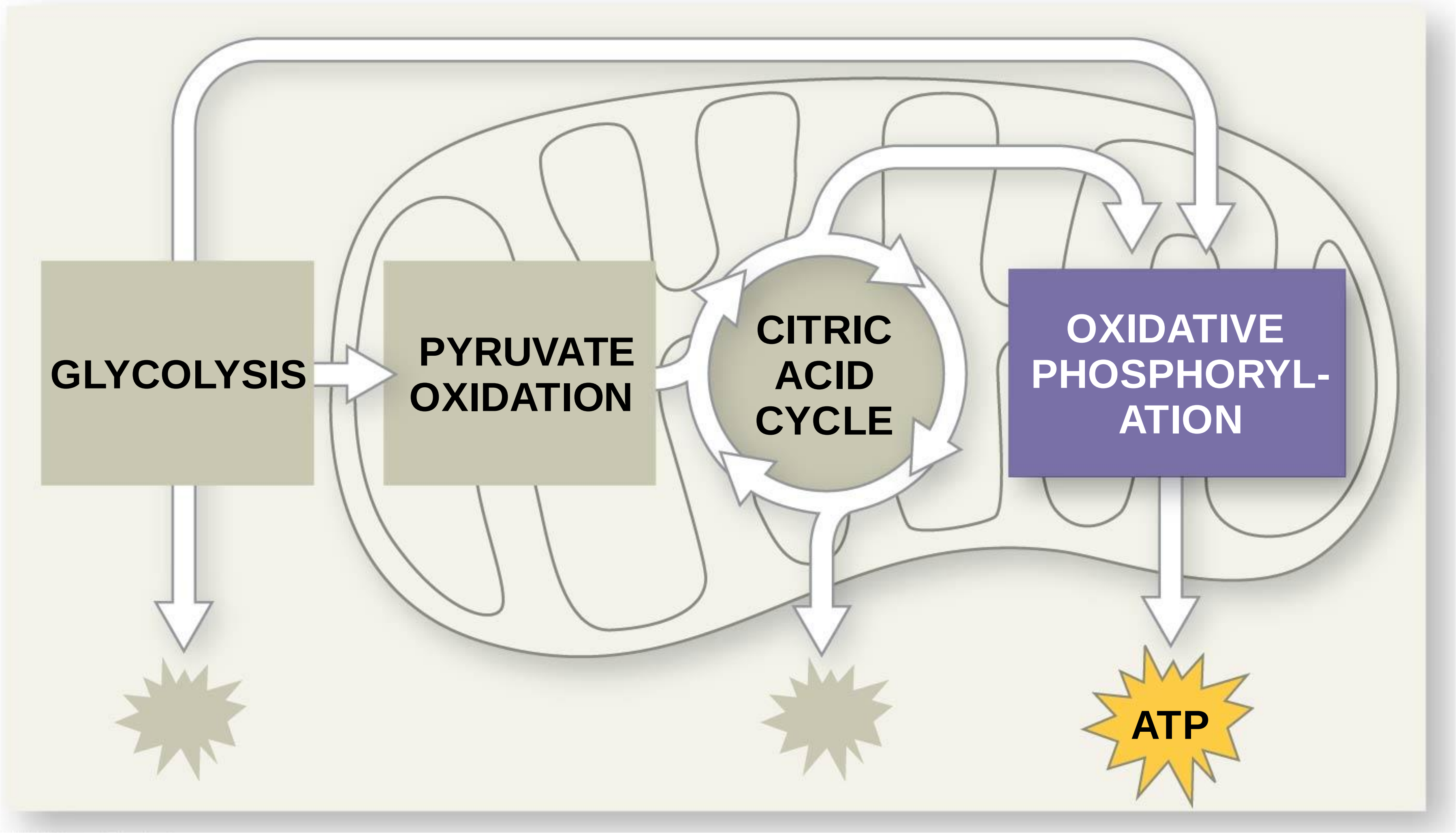
During oxidative phosphorylation, chemiosmosis couples electron transport to ATP synthesis

- Following glycolysis and the citric acid cycle, NADH and $FADH_2$ account for most of the energy extracted from food
- These two **electron carriers** donate electrons to the electron transport chain, which powers ATP synthesis via oxidative phosphorylation

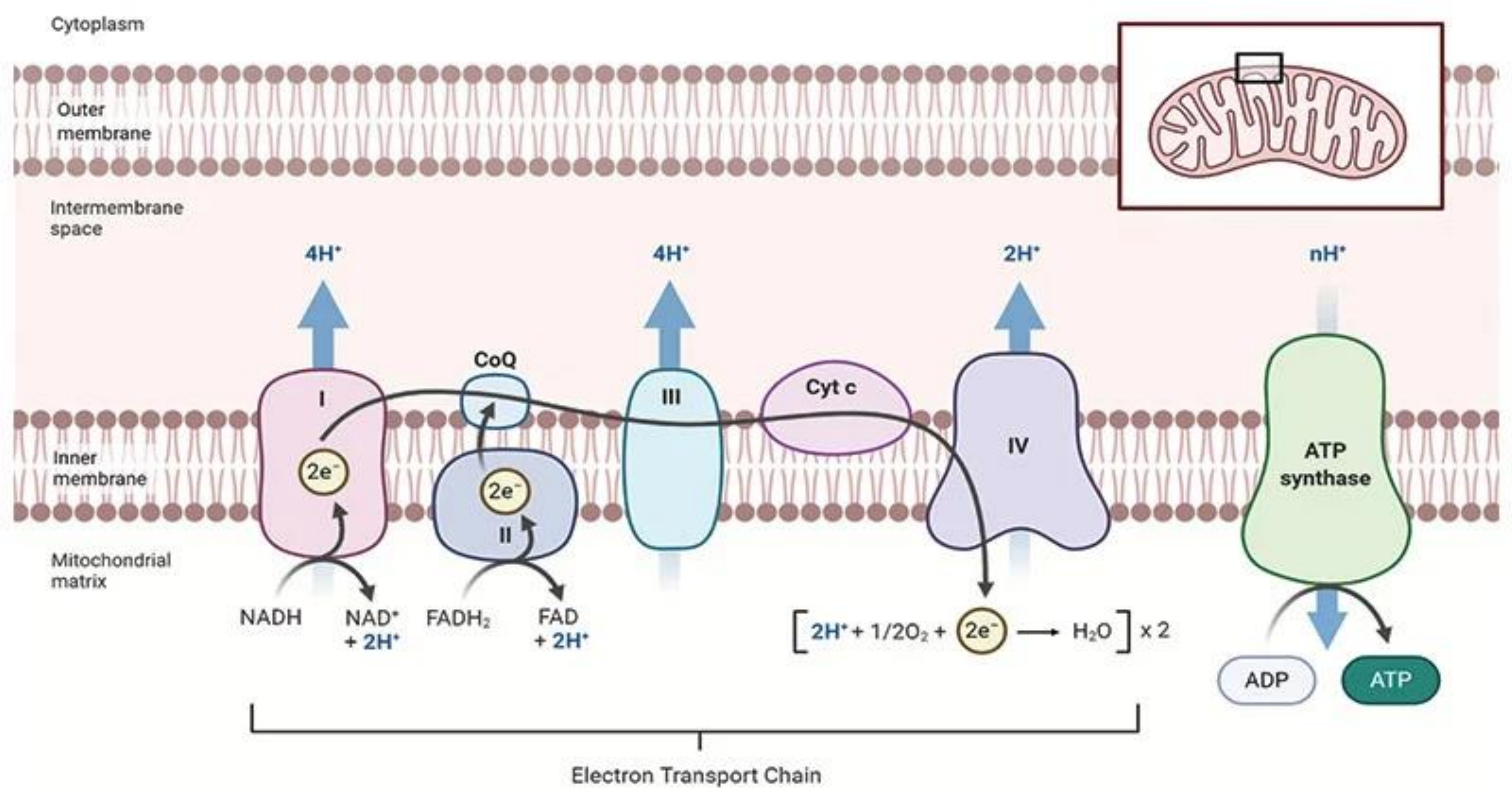
The Pathway of Electron Transport

- The electron transport chain is in the inner membrane (cristae) of the mitochondrion
- Most of the chain's components are proteins, which exist in multiprotein complexes
- Electrons drop in free energy as they go down the chain and are finally passed to O_2, forming H_2O
- Electron carriers alternate between reduced and oxidized states as they accept and donate electrons

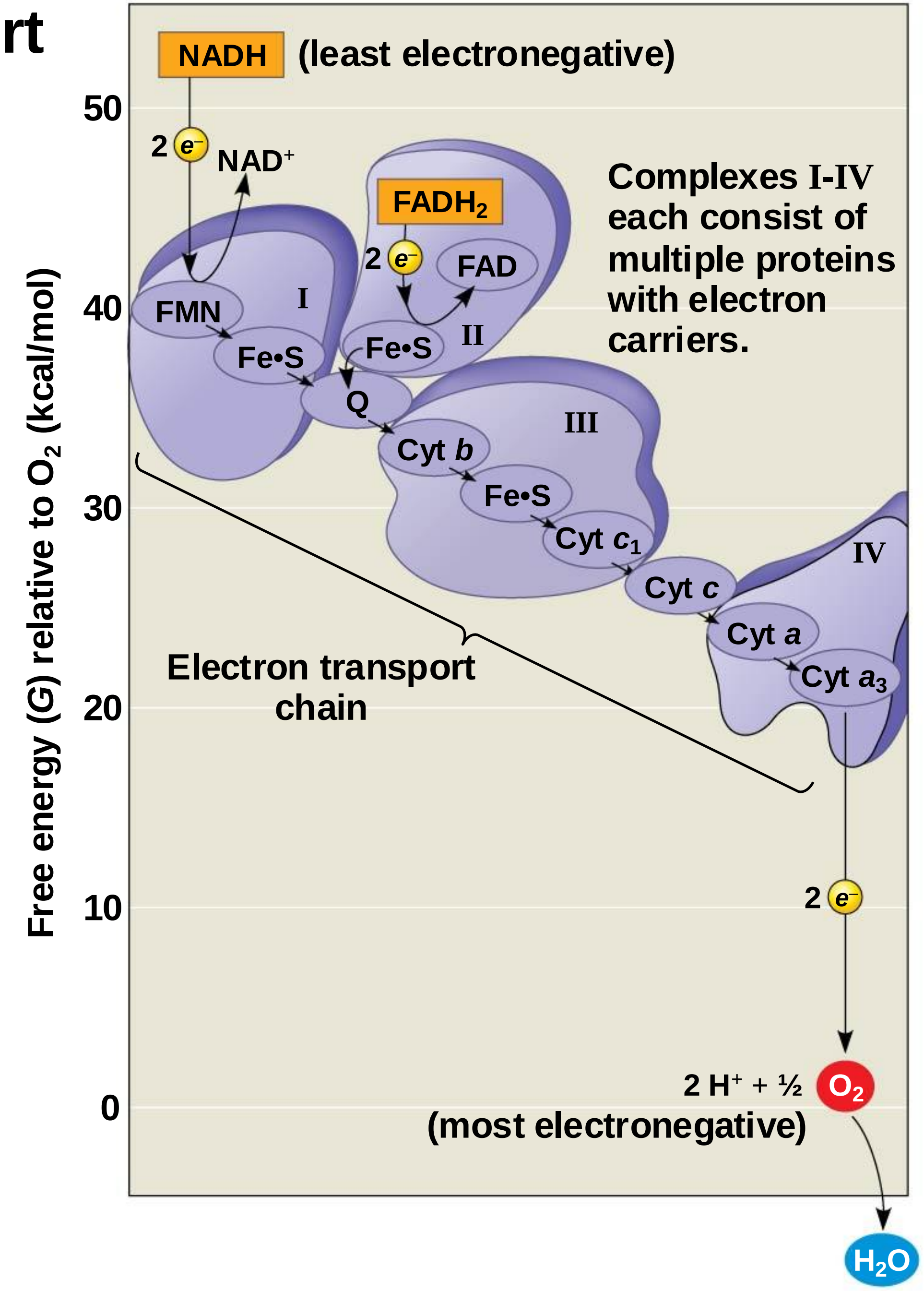
- Electrons are transferred from NADH or $FADH_2$ to the electron transport chain
- Electrons are passed through a number of proteins including **cytochromes** (each with an iron atom) to O_2
- The electron transport chain generates no ATP directly
- It breaks the large free-energy drop from food to O_2 into smaller steps that release energy in manageable amounts


GLYCOLYSIS
PYRUVATE OXIDATION
CITRIC ACID CYCLE
OXIDATIVE PHOSPHORYL-ATION
ATP

Electron transport chain



Free-energy change during electron transport



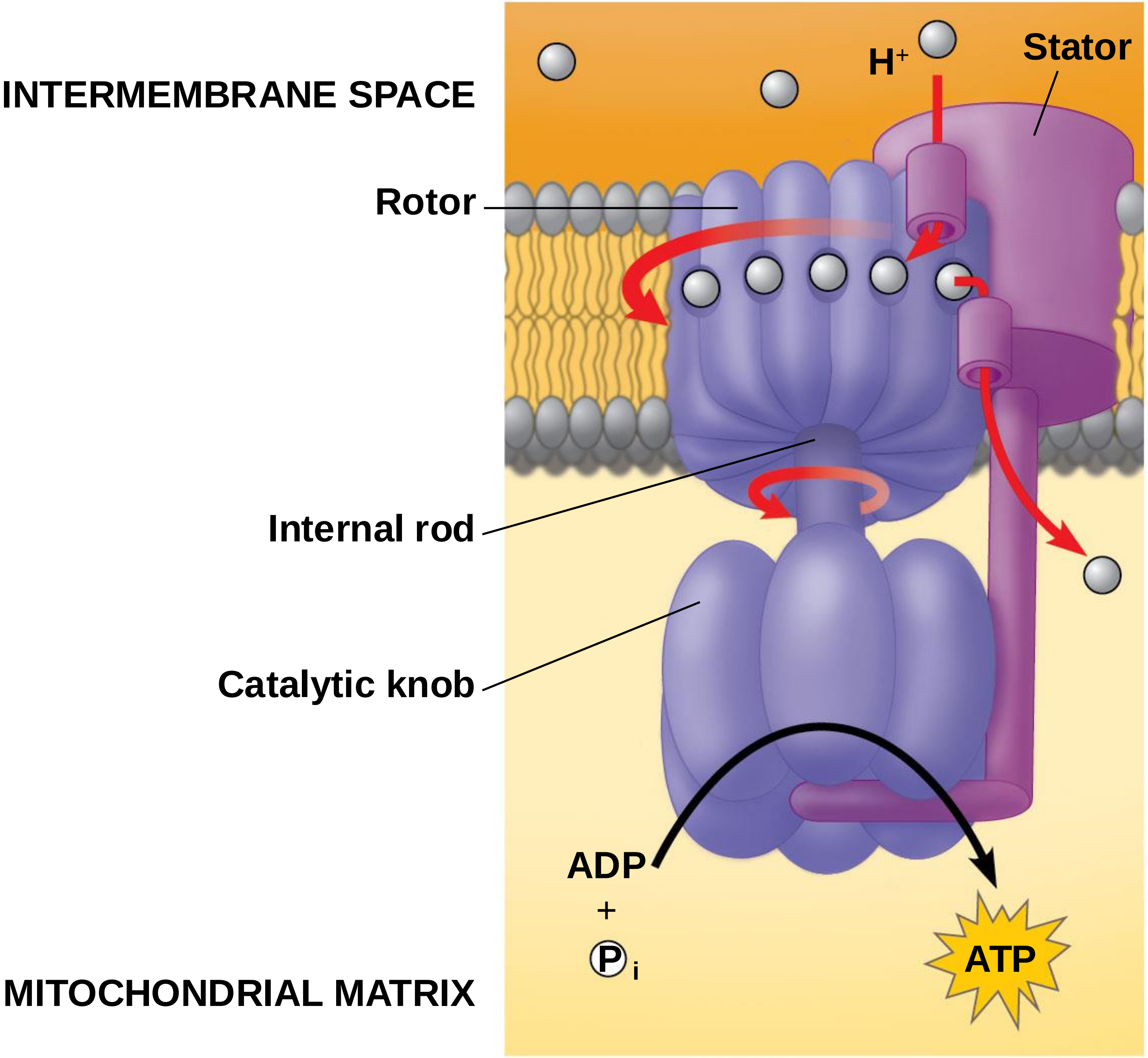
Complexes I-IV each consist of multiple proteins with electron carriers.

Chemiosmosis: The Energy-Coupling Mechanism

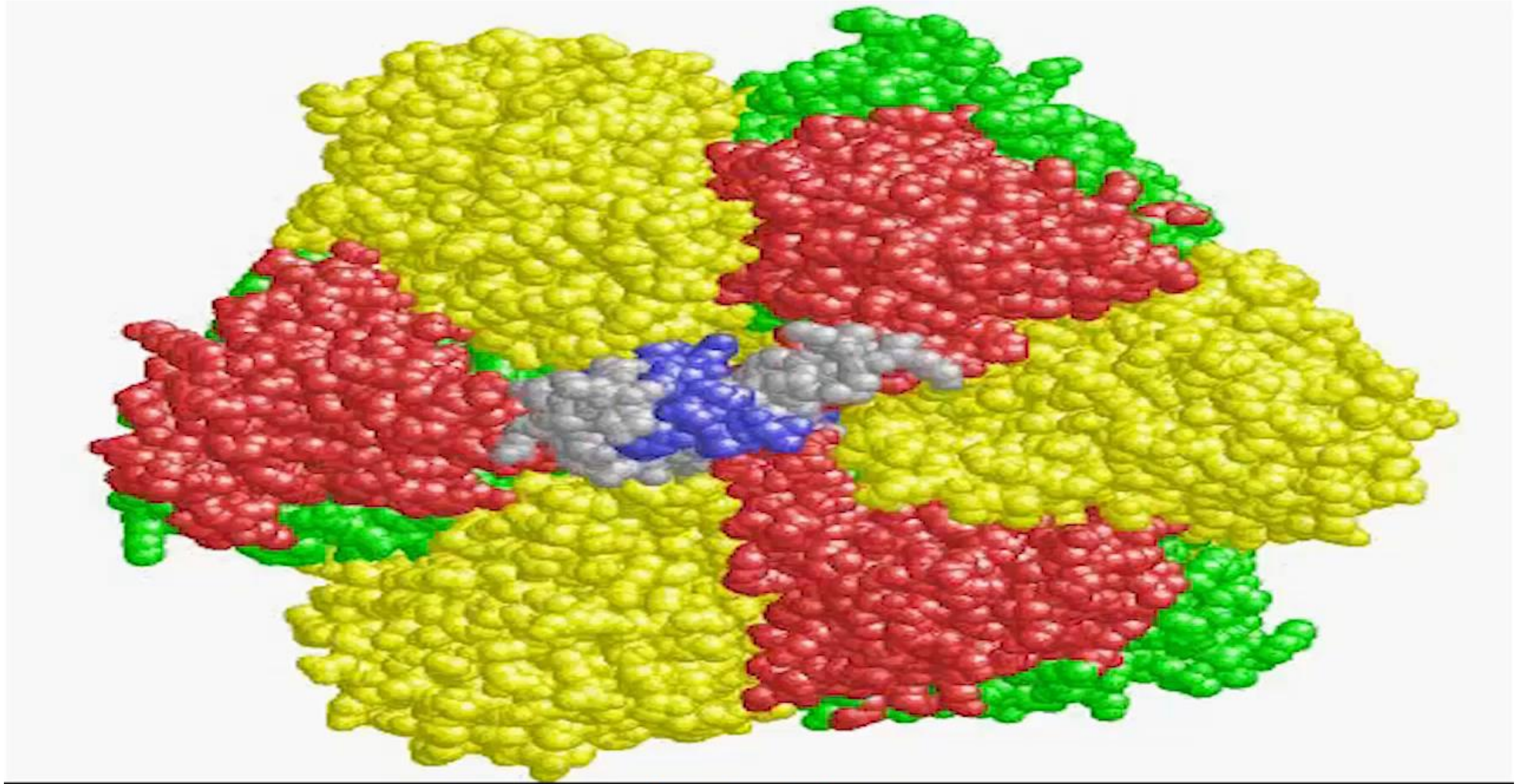
- The energy released as electrons are passed down the electron transport chain is used to pump H^+ from the mitochondrial matrix to the intermembrane space
- H^+ then moves down its concentration gradient back across the membrane, passing through the protein complex **ATP synthase**

- H^+ moves into binding sites on the rotor of ATP synthase, causing it to spin in a way that catalyzes phosphorylation of ADP to ATP
- This is an example of **chemiosmosis**, the use of energy in a H^+ gradient to drive cellular work

ATP synthase



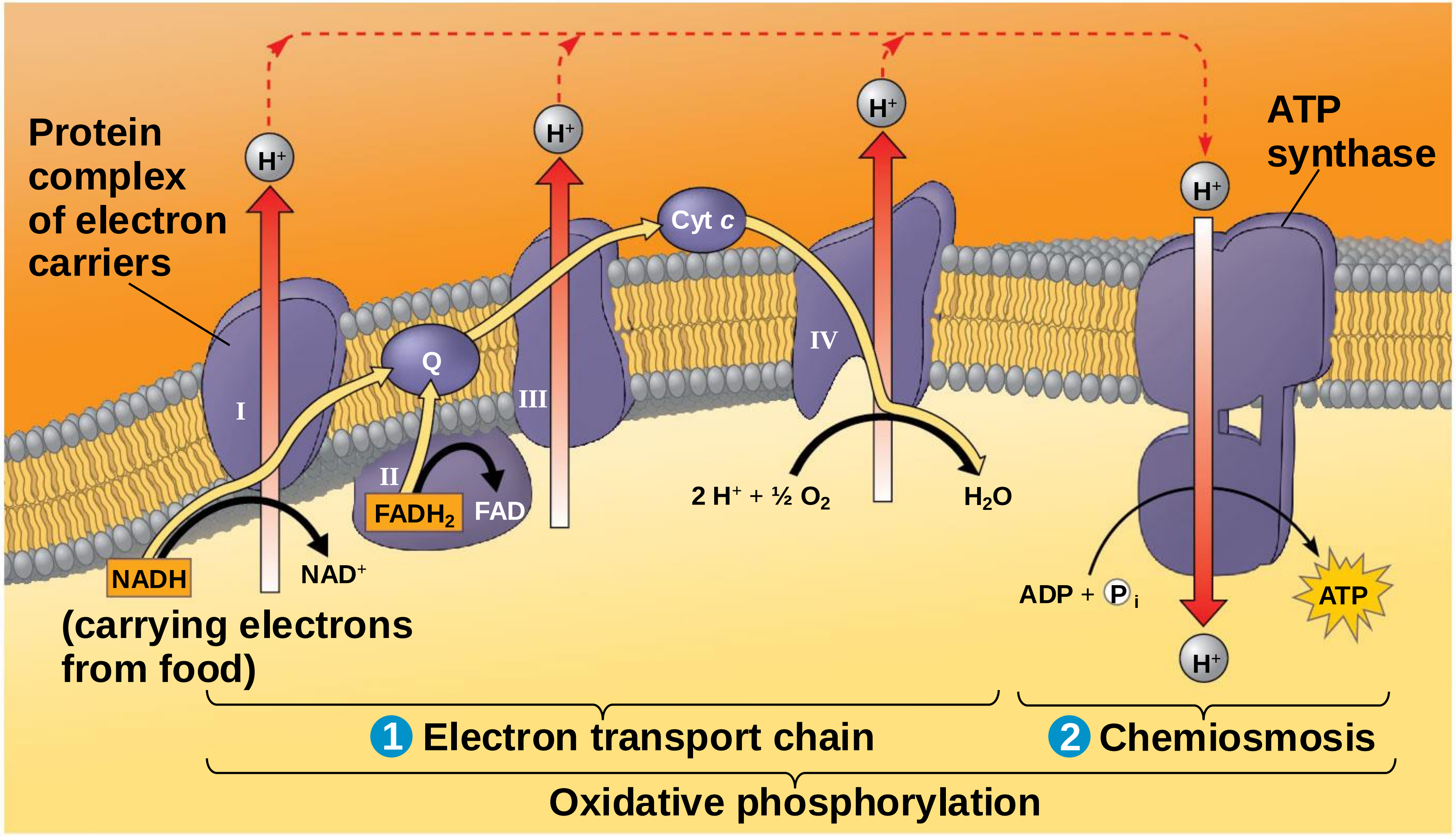
ATP Synthase 3-D Structure, Top View



A top view of alpha3-beta3-gamma
By Hongyun Wang & George Oster, U.C.Berkeley

- Certain electron carriers in the electron transport chain accept and release H^+ along with the electrons
- In this way, the energy stored in a H^+ gradient across a membrane couples the redox reactions of the electron transport chain to ATP synthesis
- The H^+ gradient is referred to as a **proton-motive force**, emphasizing its capacity to do work

Chemiosmosis couples the electron transport chain to ATP synthesis



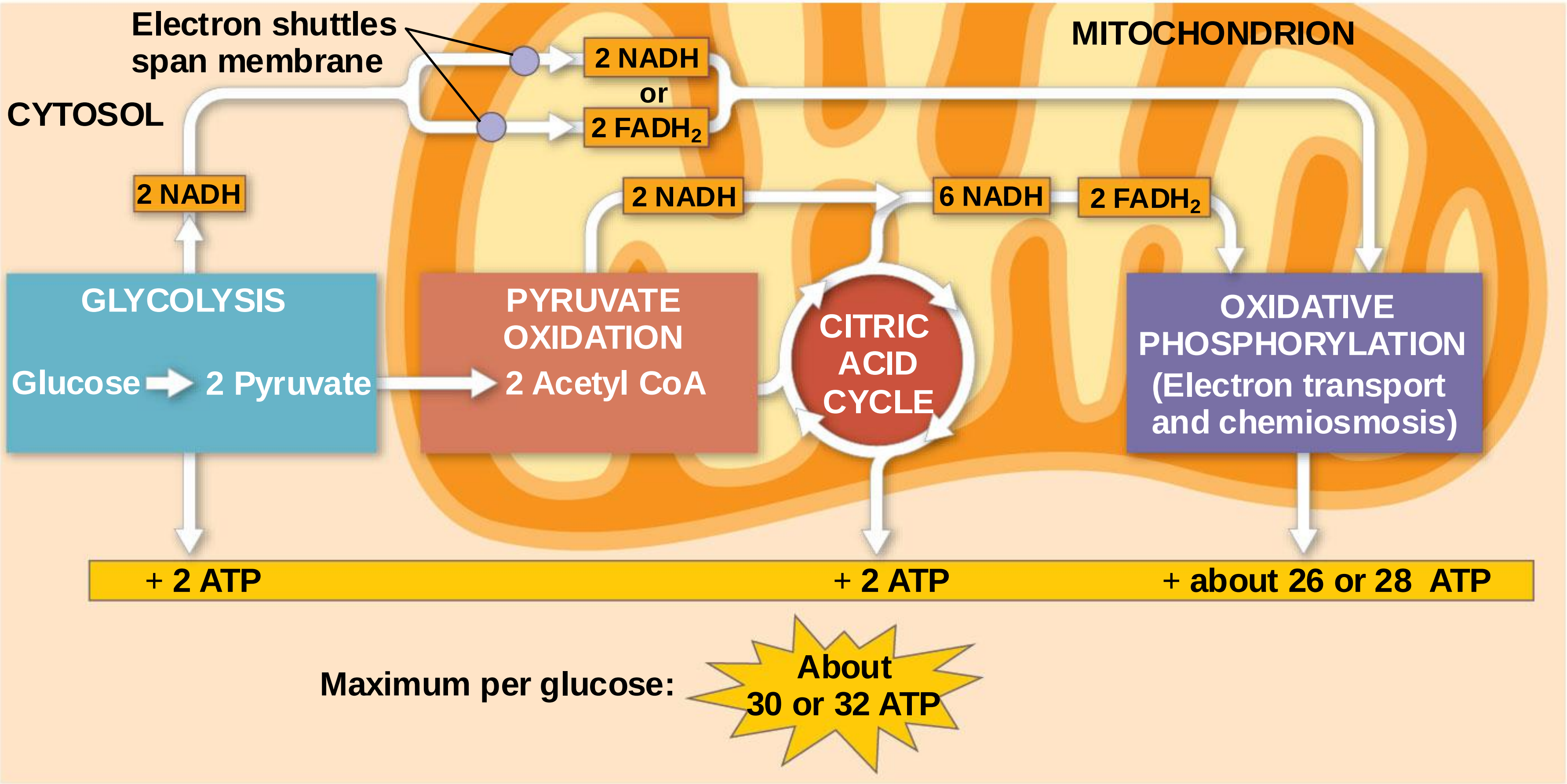
An Accounting of ATP Production by Cellular Respiration

- During cellular respiration, most energy flows in this sequence:

  glucose → NADH → electron transport chain → proton-motive force → ATP

- About 34% of the energy in a glucose molecule is transferred to ATP during cellular respiration, making about 32 ATP
- The rest of the energy is lost as heat

ATP yield per molecule of glucose at each stage of cellular respiration



- There are three reasons why the number of ATP is not known exactly
  1. Photophosphorylation and the redox reactions are not directly coupled; the ratio of NADH to ATP molecules is not a whole number
  2. ATP yield varies depending on whether electrons are passed to NAD^+ or FAD in the mitochondrial matrix
  3. The proton-motive force is also used to drive other kinds of work

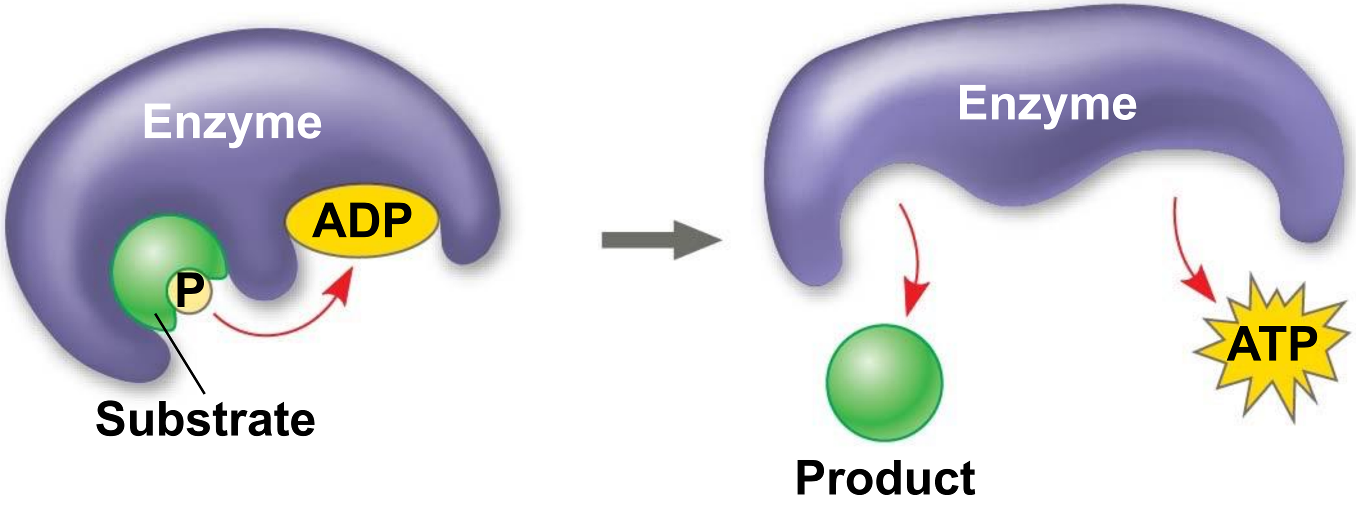
Zooming into
cellular respiration: fermentation

Fermentation and anaerobic respiration enable cells to produce ATP without oxygen

- Most cellular respiration depends on electronegative oxygen to pull electrons down the transport chain
- Without oxygen, the electron transport chain will cease to operate
- In that case, glycolysis couples with anaerobic respiration or fermentation to produce ATP

Anaerobic respiration vs. fermentation

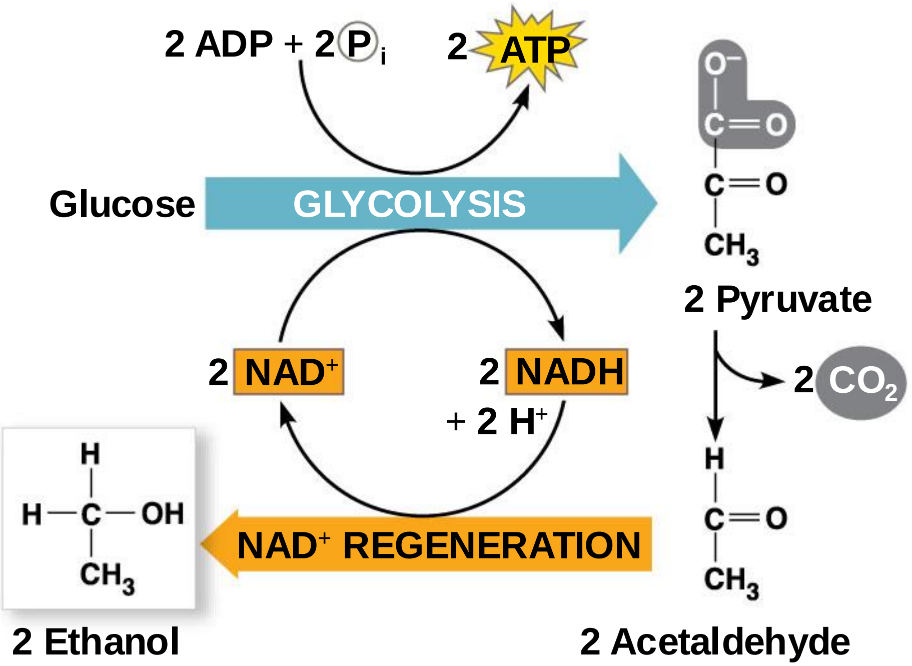
- Anaerobic respiration uses an electron transport chain with a final electron acceptor other than oxygen, for example, sulfate
- Fermentation uses substrate-level phosphorylation instead of an electron transport chain to generate ATP



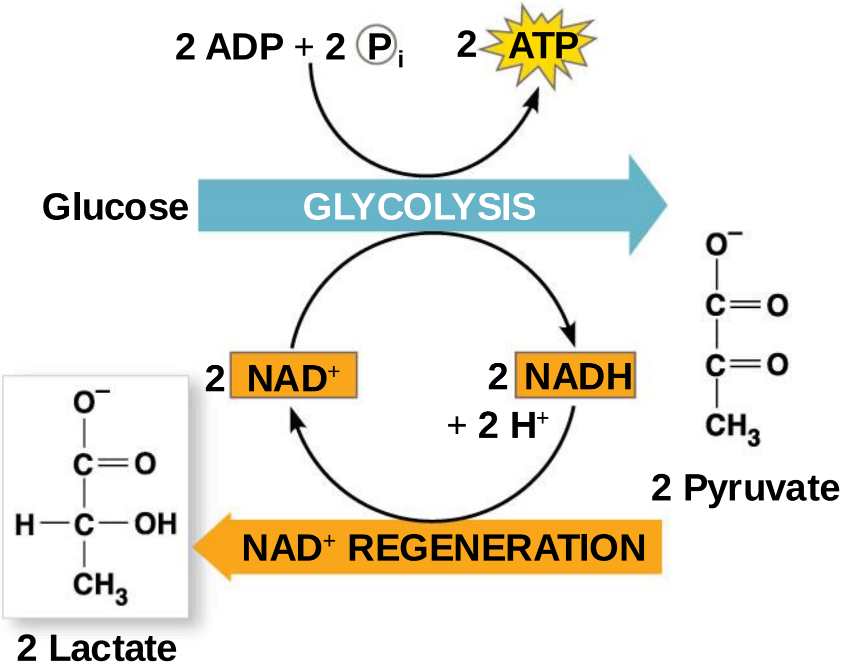
Types of Fermentation

- Fermentation consists of glycolysis plus other reactions that regenerate NAD^+, which can be reused by glycolysis
- Two common types are alcohol fermentation and lactic acid fermentation

Alcohol fermentation

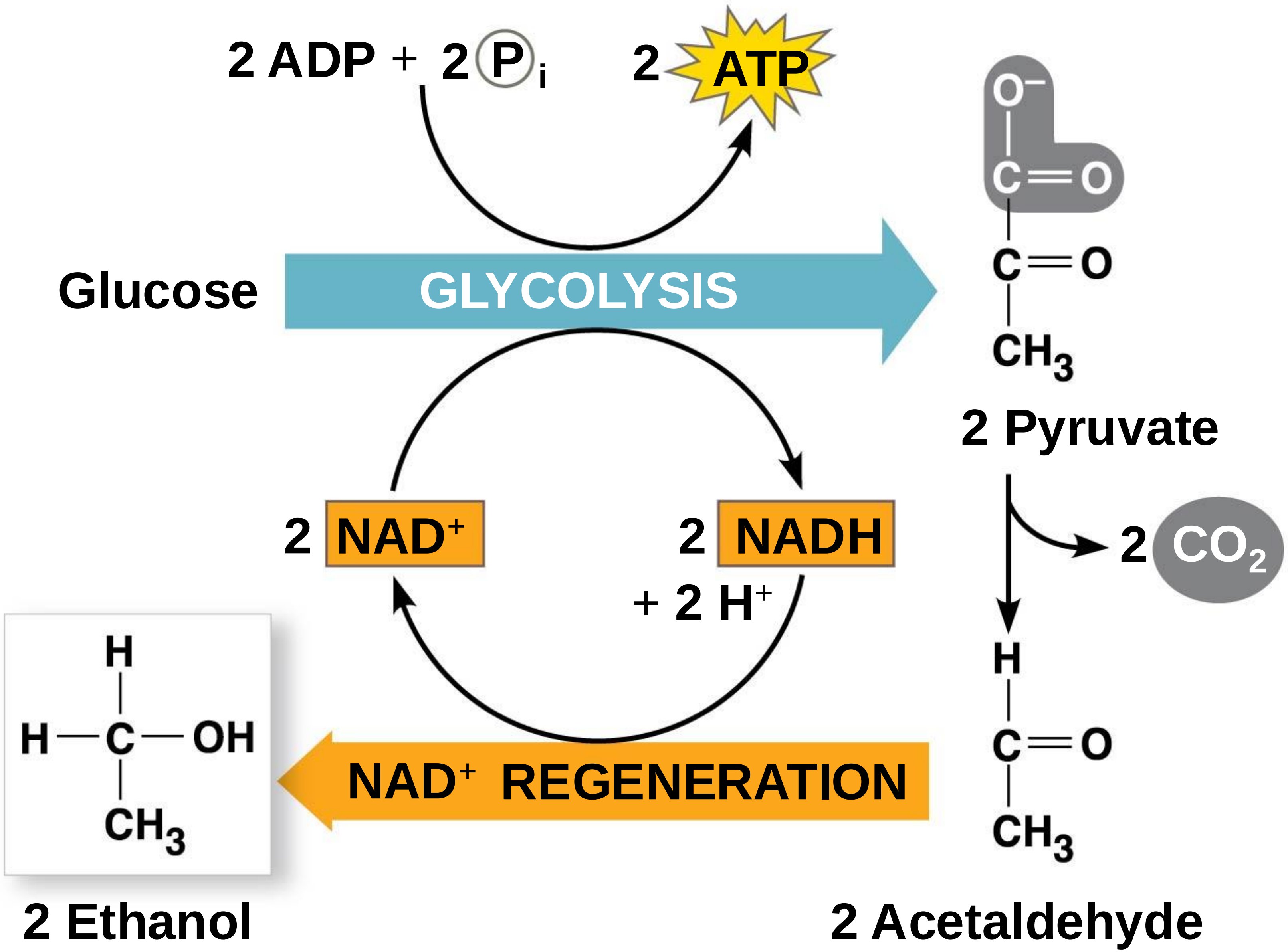


Lactic acid fermentation



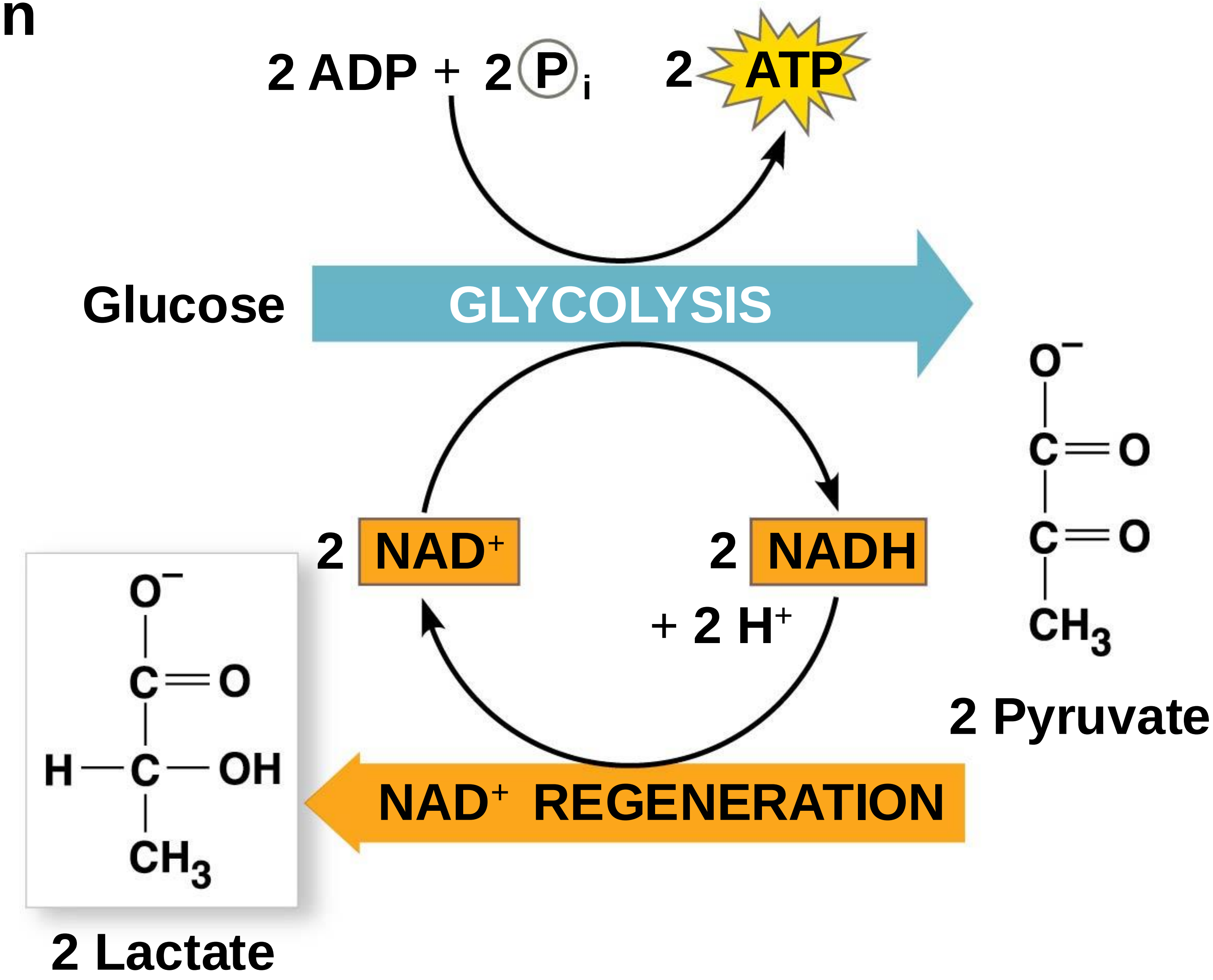
- In **alcohol fermentation**, pyruvate is converted to ethanol in two steps
  - The first step releases CO_2 from pyruvate
  - The second step produces NAD^+ and ethanol
- Alcohol fermentation by yeast is used in brewing, winemaking, and baking

Alcohol fermentation



- In **lactic acid fermentation**, pyruvate is reduced by NADH, forming NAD^+ and lactate as end products, with no release of CO_2
- Lactic acid fermentation by some fungi and bacteria is used to make cheese and yogurt
- Human muscle cells use lactic acid fermentation to generate ATP during strenuous exercise when O_2 is scarce

Lactic acid fermentation



2 ADP + 2 Ⓟ$_i$

2 ATP

Glucose

GLYCOLYSIS

2 NAD$^+$

2 NADH

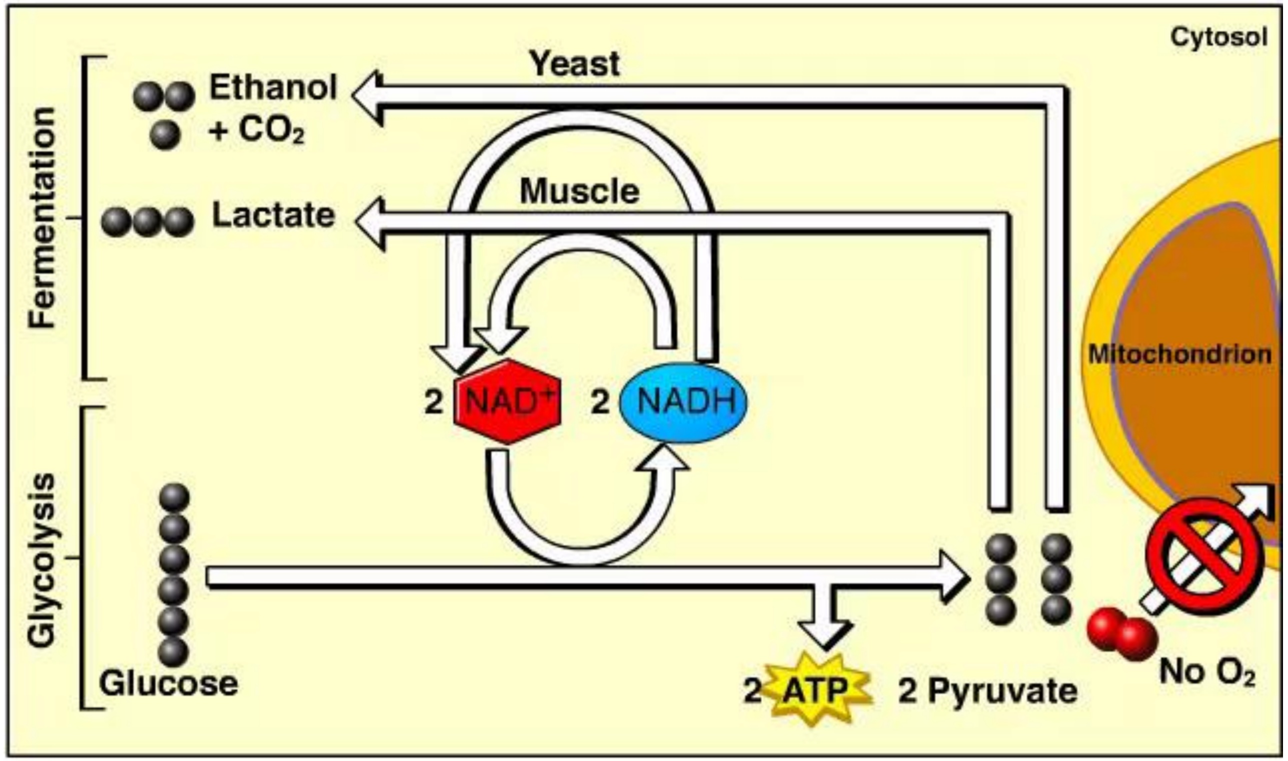
+ 2 H$^+$

NAD$^+$ REGENERATION

2 Pyruvate

2 Lactate

Fermentation Overview



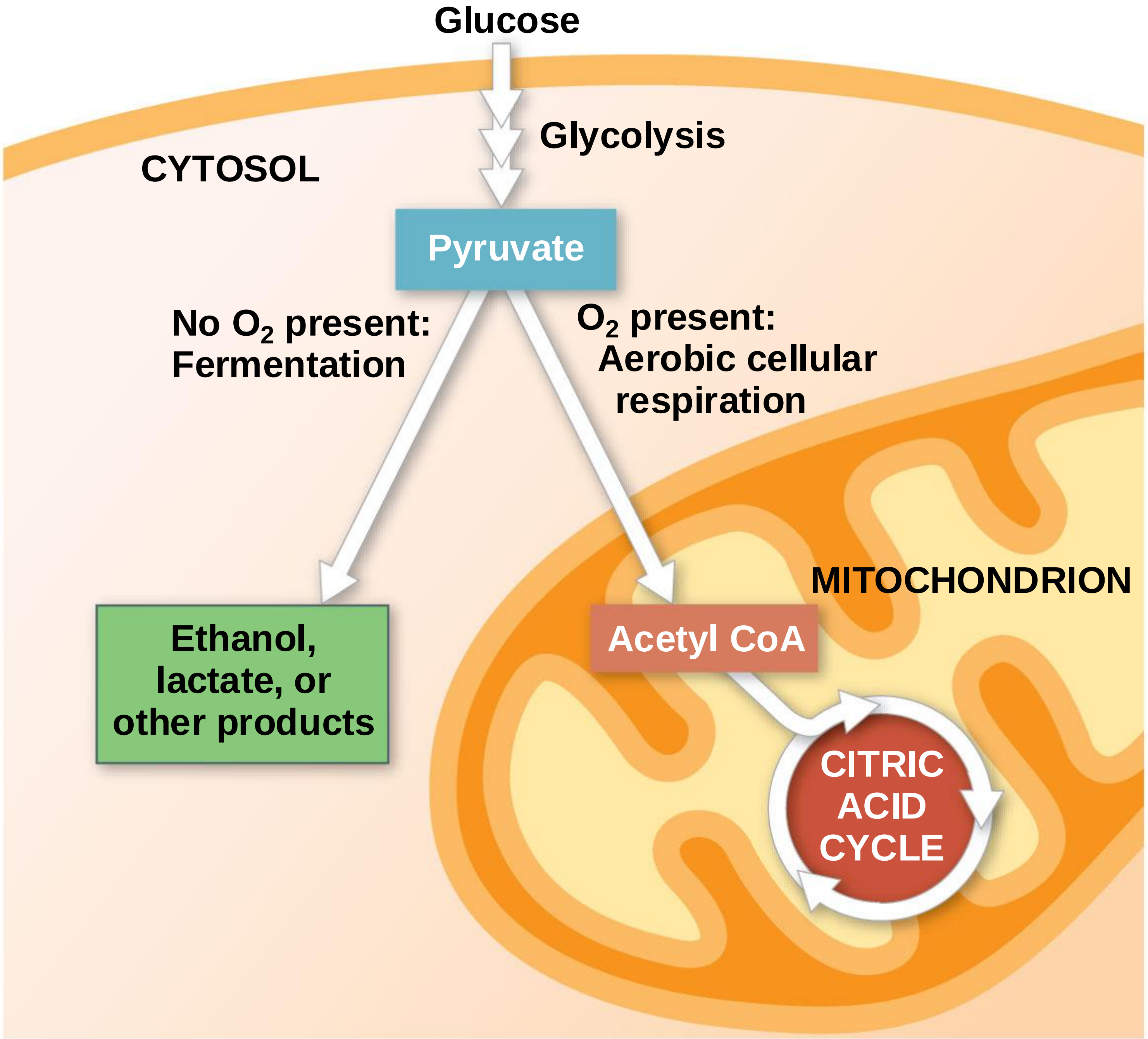
Comparing Fermentation with Anaerobic and Aerobic Respiration

- All use glycolysis (net ATP = 2) to oxidize glucose and harvest the chemical energy of food
- In all three, NAD^+ is the oxidizing agent that accepts electrons during glycolysis

- The processes have different mechanisms for oxidizing NADH to NAD^+:
    - In fermentation, an organic molecule (such as pyruvate or acetaldehyde) acts as a final electron acceptor
    - In cellular respiration, electrons are transferred to the electron transport chain
- Cellular respiration produces 32 ATP per glucose molecule; fermentation produces 2 ATP per glucose molecule

- **Obligate anaerobes** carry out fermentation or anaerobic respiration and cannot survive in the presence of O_2
- Yeast and many bacteria are **facultative anaerobes**, meaning that they can survive using either fermentation or cellular respiration
- In a facultative anaerobe, pyruvate is a fork in the metabolic road that leads to two alternative catabolic routes

Pyruvate is key for catabolism



The Evolutionary Significance of Glycolysis

- Glycolysis is an ancient process
- Early prokaryotes likely used glycolysis to produce ATP before O_2 accumulated in the atmosphere
- Used in both cellular respiration and fermentation, it is the most widespread metabolic pathway on Earth
- This pathway occurs in the cytosol so does not require the membrane-bound organelles of eukaryotic cells

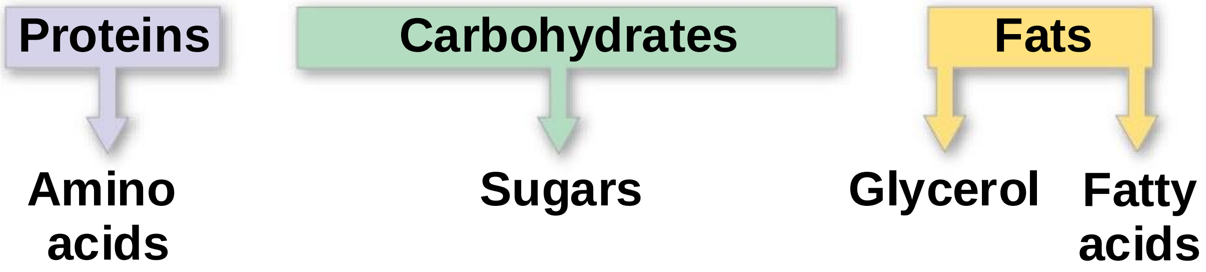
Glycolysis and the citric acid cycle connect to many other metabolic pathways

- Gycolysis and the citric acid cycle are major intersections to various catabolic and anabolic pathways

The Versatility of Catabolism

- Catabolic pathways funnel electrons from many kinds of organic molecules into cellular respiration
- Glycolysis accepts a wide range of carbohydrates including starch, glycogen, and several disaccharides
- Proteins that are used for fuel must be digested to amino acids and their amino groups must be removed

- Fats are digested to glycerol (used to produce compounds needed for glycolysis) and fatty acids
- Fatty acids are broken down by **beta oxidation** and yield acetyl CoA, NADH, and $FADH_2$
- An oxidized gram of fat produces more than twice as much ATP as an oxidized gram of carbohydrate



Proteins

Carbohydrates

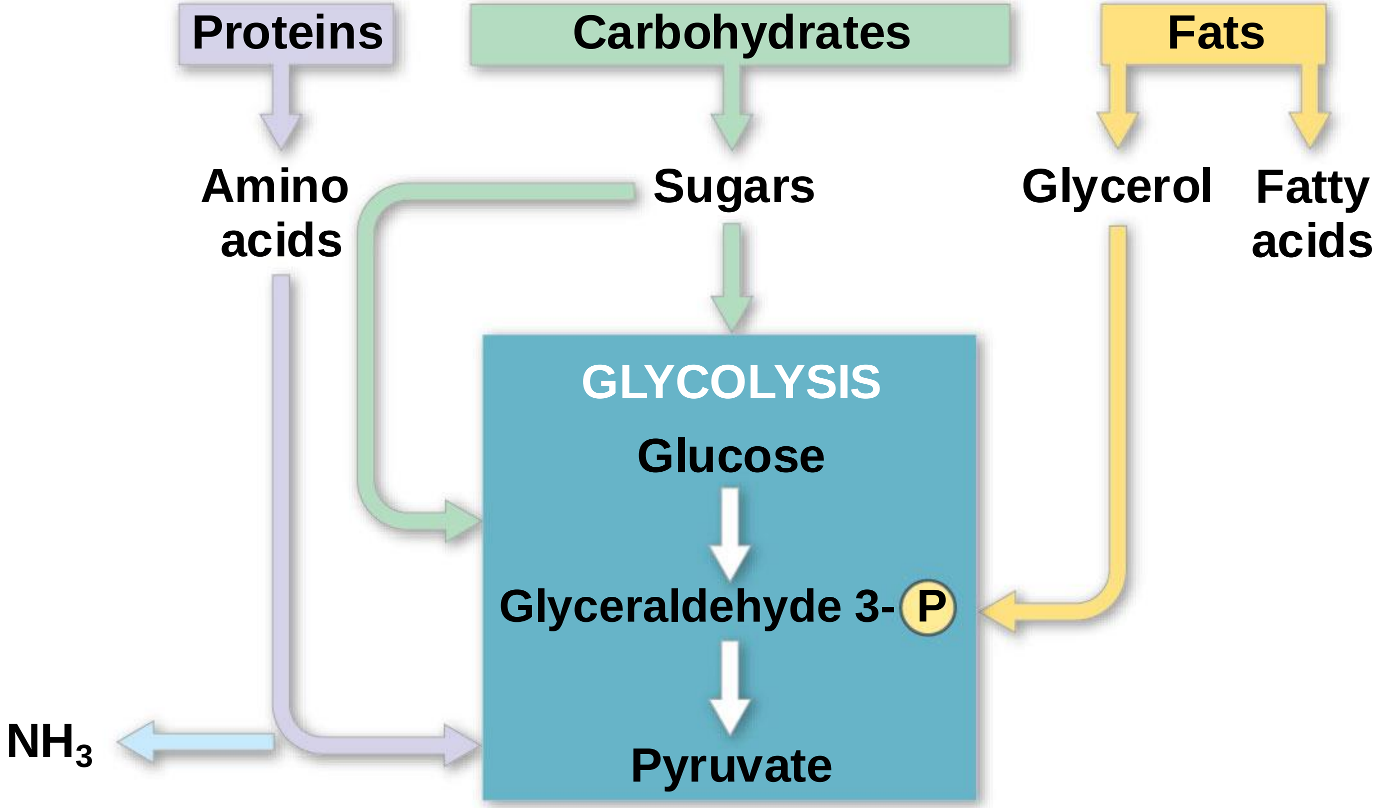
Fats

Amino acids

Sugars

Glycerol

Fatty acids



Proteins

Carbohydrates

Fats

Amino acids

Sugars

Glycerol

Fatty acids

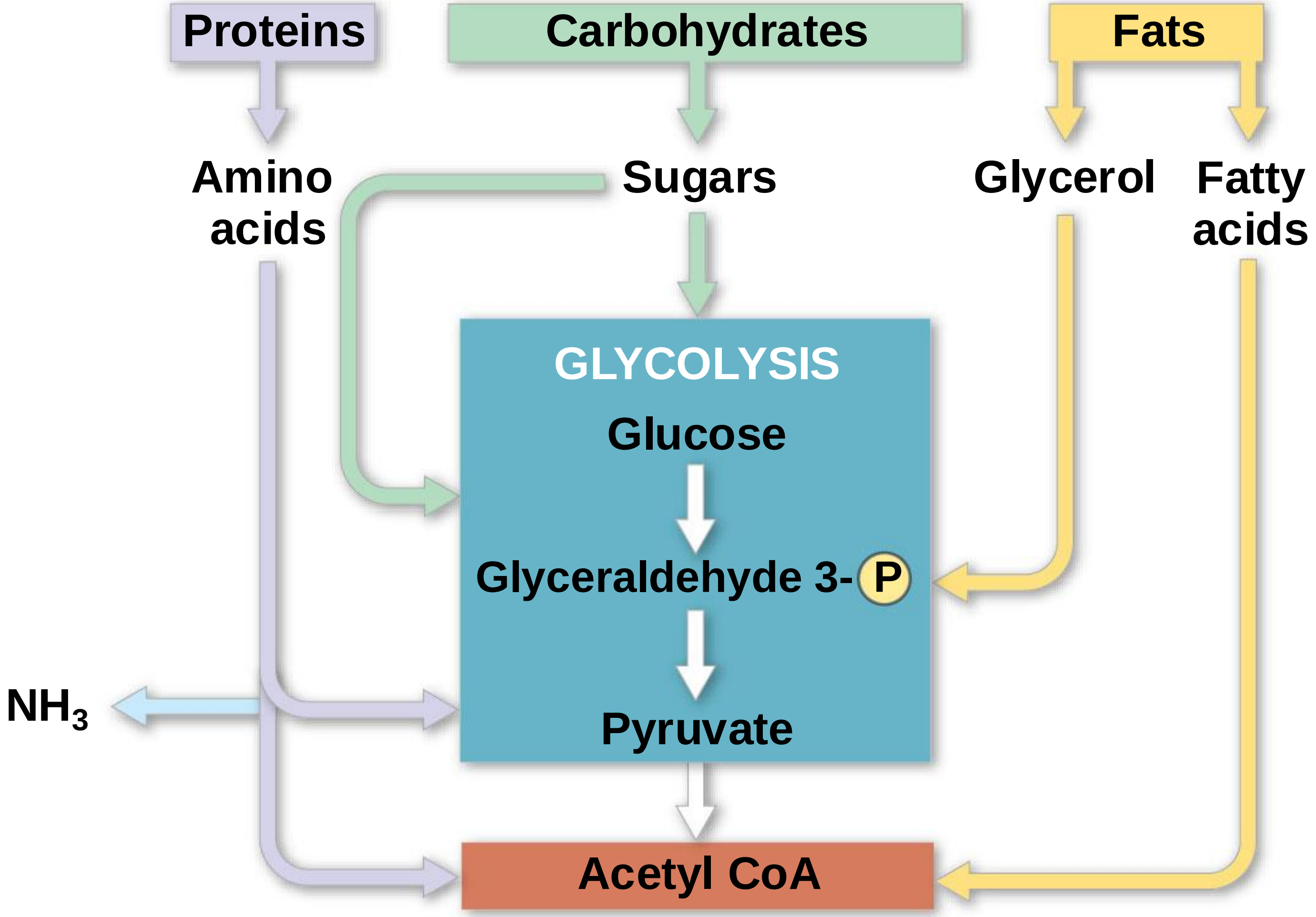
GLYCOLYSIS

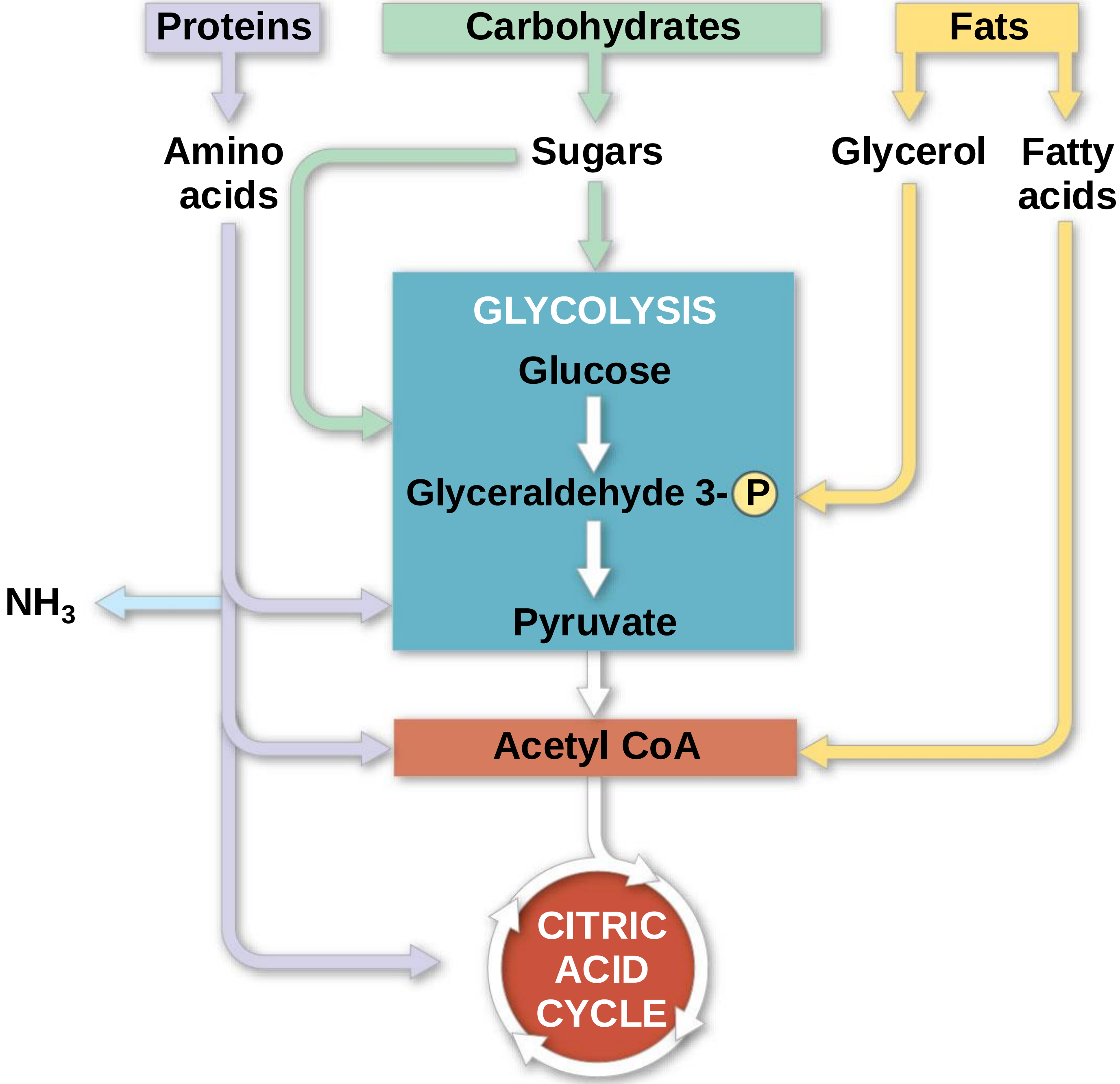
Glucose

Glyceraldehyde 3-Ⓟ

Pyruvate

NH_3


Proteins
Carbohydrates
Fats
Amino acids
Sugars
Glycerol
Fatty acids
GLYCOLYSIS
Glucose
Glyceraldehyde 3-P
Pyruvate
NH_3
Acetyl CoA



Proteins

Carbohydrates

Fats

Amino acids

Sugars

Glycerol

Fatty acids

GLYCOLYSIS

Glucose

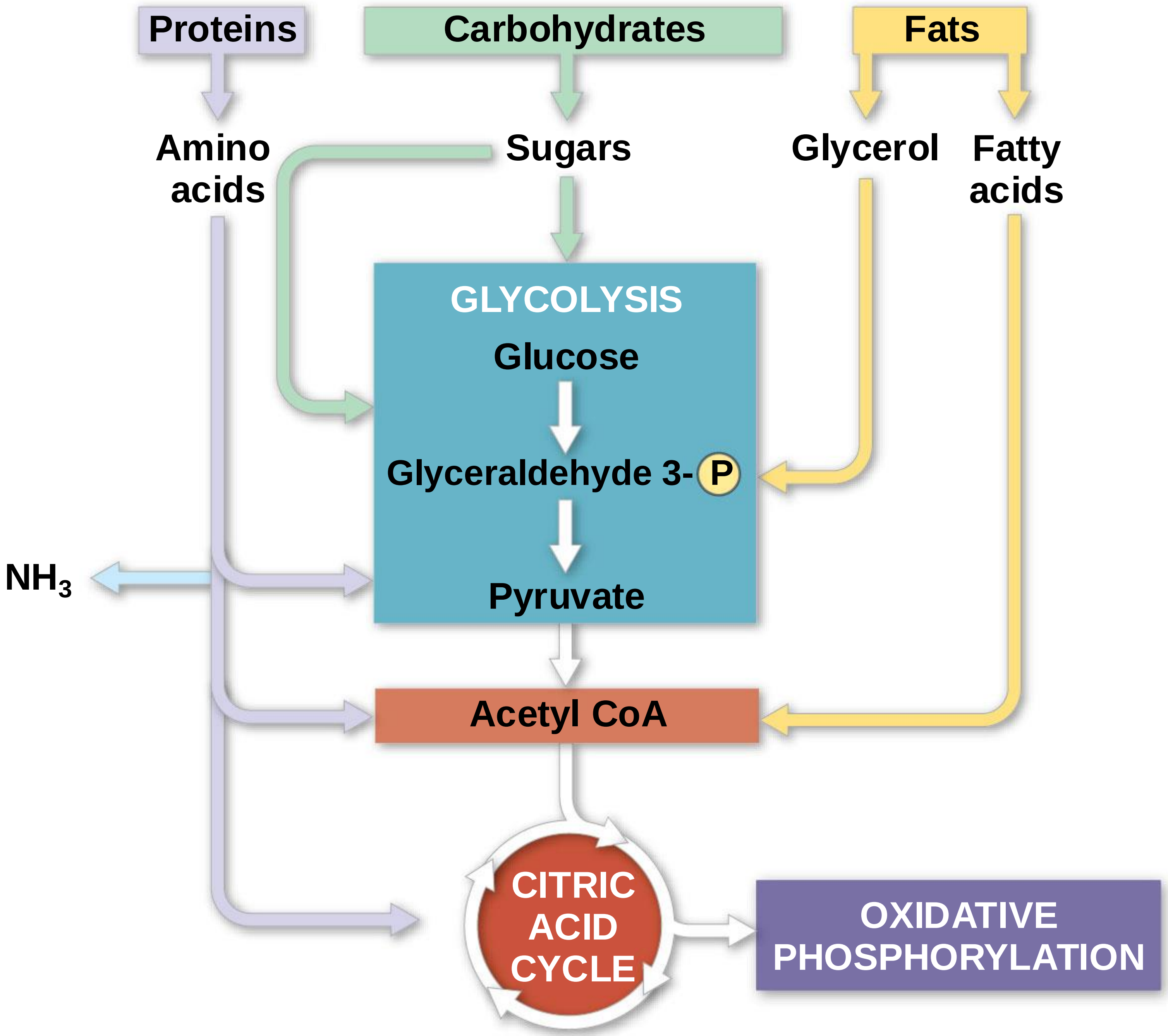
Glyceraldehyde 3-Ⓟ

Pyruvate

NH_3

Acetyl CoA

CITRIC ACID CYCLE



Proteins

Carbohydrates

Fats

Amino acids

Sugars

Glycerol

Fatty acids

GLYCOLYSIS

Glucose

Glyceraldehyde 3- **P**

Pyruvate

NH_3

Acetyl CoA

CITRIC ACID CYCLE

OXIDATIVE PHOSPHORYLATION

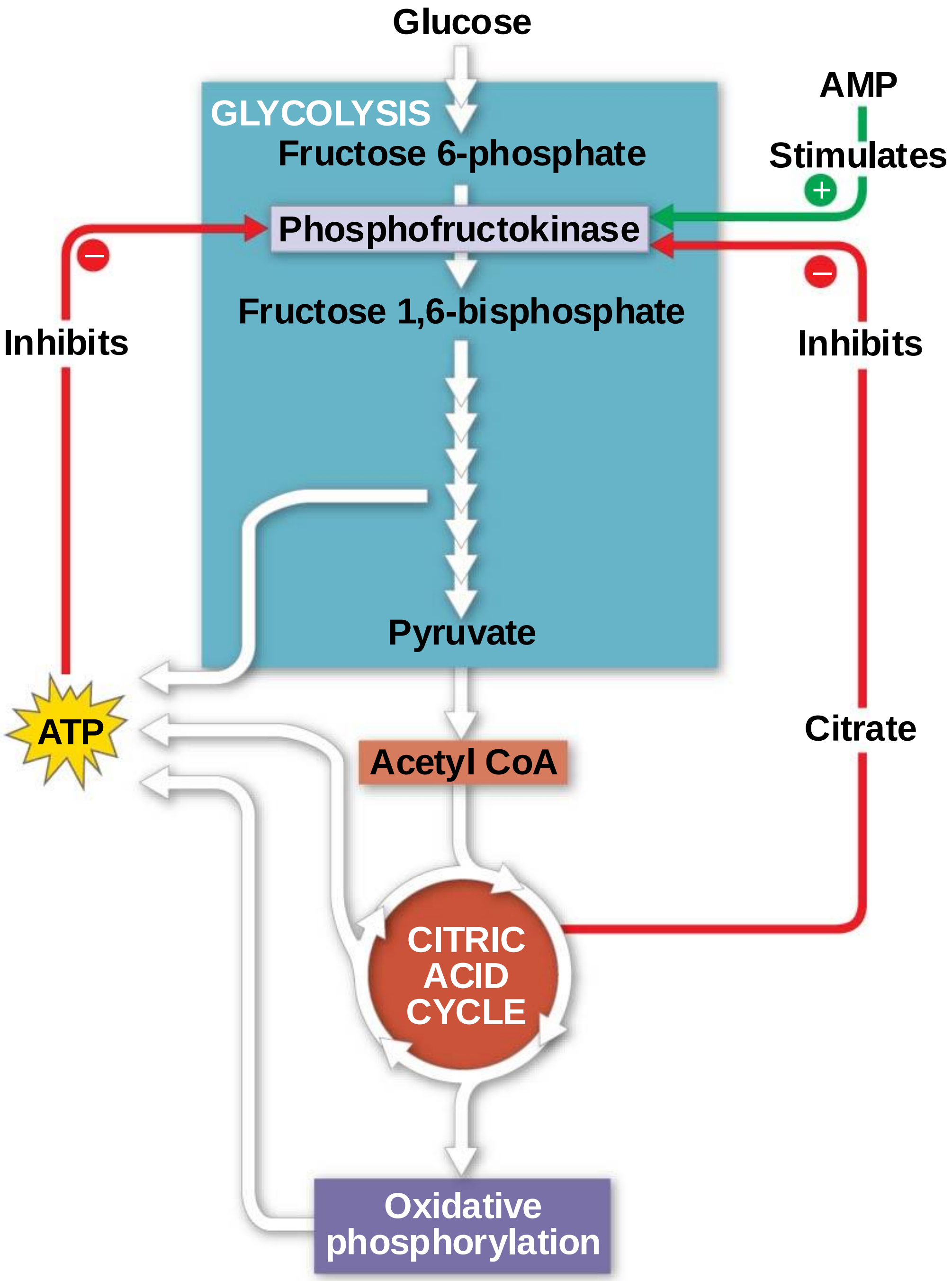
Biosynthesis (Anabolic Pathways)

- The body uses small molecules from food to build other their own molecules such as proteins
- These small molecules may come directly from food, from glycolysis, or from the citric acid cycle

Control of Cellular Respiration via Feedback Mechanisms

- Feedback inhibition is the most common mechanism for metabolic control
- If ATP concentration begins to drop, respiration speeds up; when there is plenty of ATP, respiration slows down
- Control of catabolism is based mainly on regulating the activity of enzymes at strategic points in the catabolic pathway

The control of cellular respiration

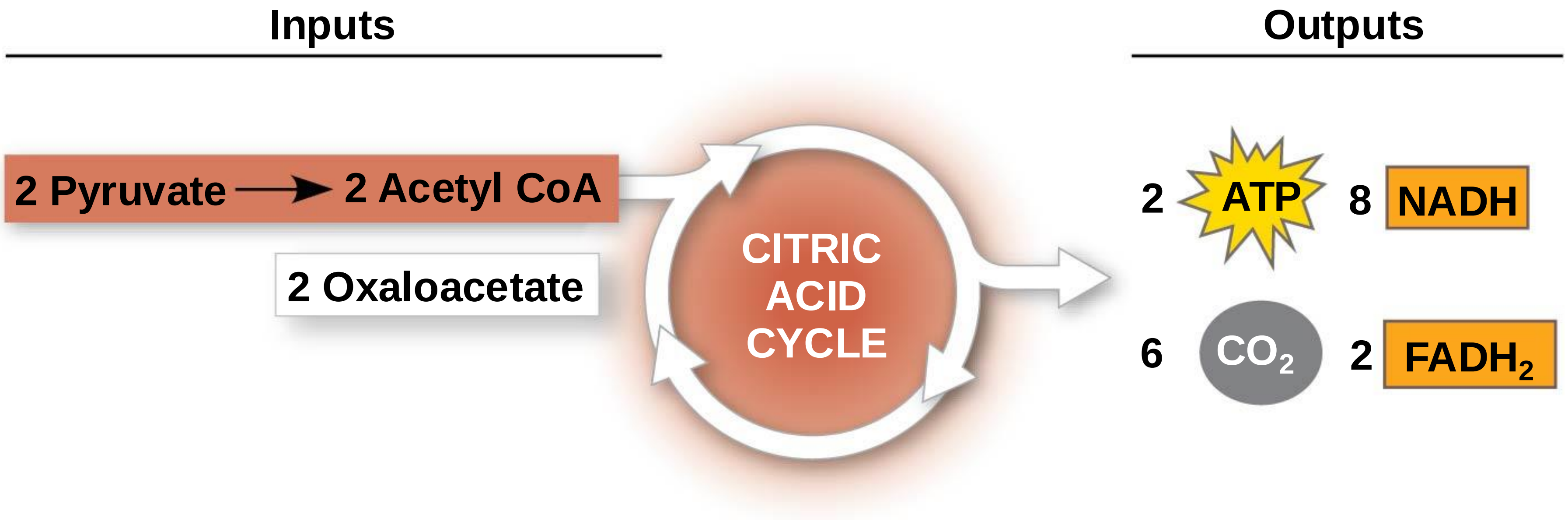


Summary: glycolysis

Inputs | **Outputs**

Glucose → GLYCOLYSIS → 2 Pyruvate + 2 ATP + 2 NADH

Summary: citric acid cycle / Krebs cycle



Inputs

2 Pyruvate → 2 Acetyl CoA

2 Oxaloacetate

CITRIC ACID CYCLE

Outputs

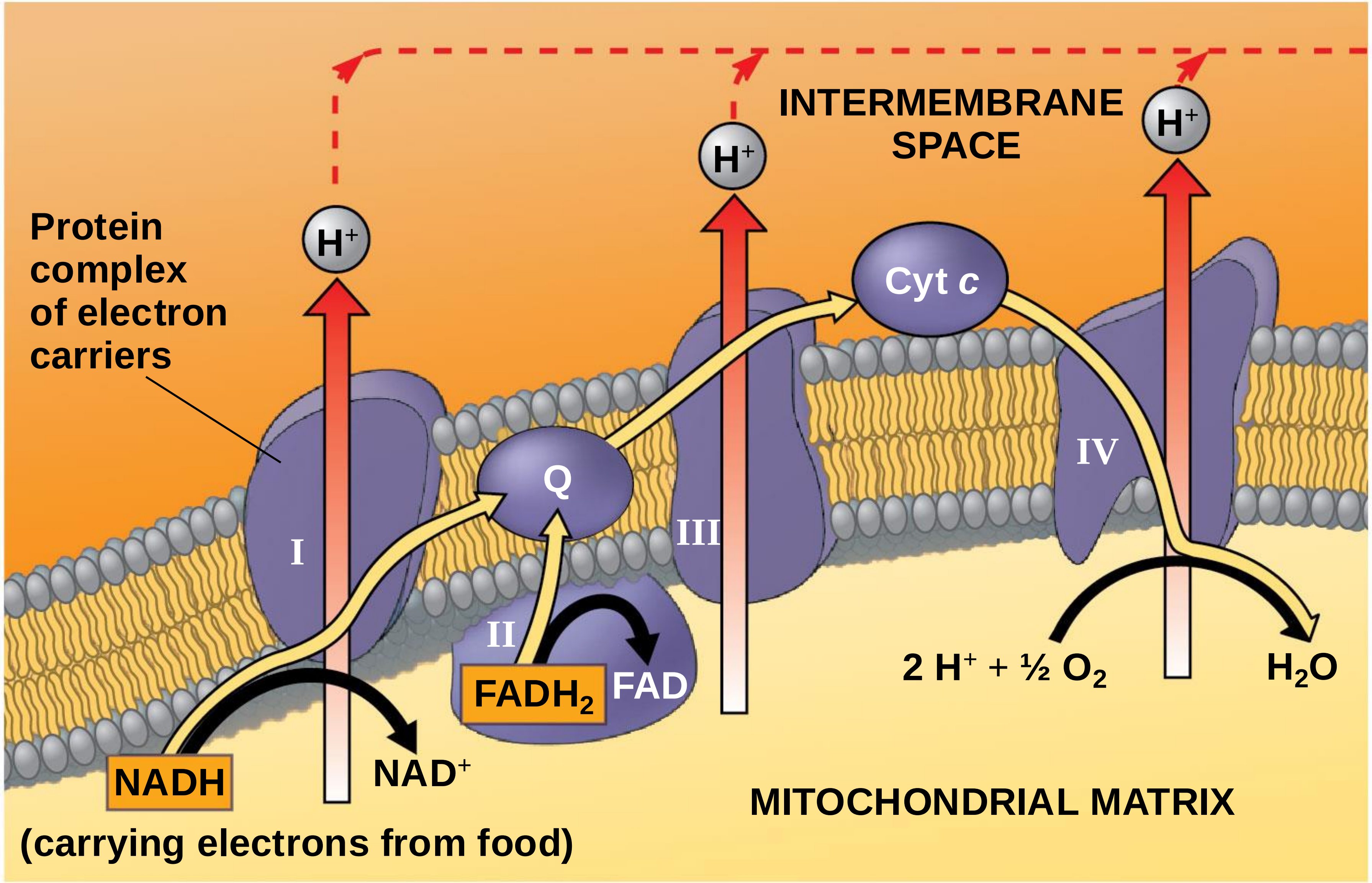
2 ATP

8 NADH

6 CO_2

2 $FADH_2$

Summary: electron transport chain



Summary: ATP synthase